nature reviews
rheumatology

July 2026

https://doi.org/10.1038/s41584-026-01390-6

20 years of progress in the classification of immune-mediated diseases

Dennis McGonagle, Daniel L. Kastner & Ivona Aksentijevich

20 years ago, the modern classification of inflammation against self was developed, wherein an immunological disease continuum was invoked, as autoimmunity alone inadequately explained the spectrum of self-directed inflammation.

In a landmark 2006 paper, a classification for immunological diseases was proposed[1] that presented immunological diseases as an 'autoinflammatory–autoimmune continuum'. That paper represented the evolution of the field since Daniel Kastner first introduced the concept of autoinflammation in 1999. In the years following the publication of that article, the field has again evolved considerably, and research has provided invaluable insights into these complex immunological diseases.

The discovery of Toll-like receptors in the mid-1990s and the description of pathogen-associated molecular patterns and danger-associated molecular patterns represented a major advance in the field of immunology; however, these discoveries were not immediately used to inform the understanding of innate immune disease. From 1997 onwards, the Kastner laboratory and others investigating hereditary periodic fevers identified the underlying mutations of genes linked to familial Mediterranean fever (*MEFV*) and TNF-receptor-associated periodic syndrome (*TNFR1*), thus confirming dysregulation of the IL-1 and TNF pathways, two pivotal cytokines that are key to innate immunity, in these diseases[2]. This work led to coining of the term 'autoinflammation'[2,3]. Further autosomal dominant autoinflammatory disorders described in the early 2000s were subsequently linked to multimeric cytosolic complexes, termed inflammasomes, which, together with dysregulated IL-1 expression, not only explained these hereditary periodic fevers but also provided a molecular basis for crystal disease, including gout and pseudogout, further cementing the autoinflammation concept[4,5]. From there, the understanding of autoinflammatory disease, and especially that it represented innate immunity dysregulation, grew exceptionally, with relevance for many poorly defined inflammatory disorders, and the introduction of targeted anti-IL-1 therapy transformed the lives of patients. When the immunological disease continuum concept was published in 2006 (ref. 1), it was initially not greeted with much enthusiasm, but this has since become a landmark paper, owing to the emergence of many novel autoinflammatory and autoimmune diseases, and it also overlaps both components of adaptive and innate immune dysregulation that that fitted neatly into the scheme.

The MHC-I-opathy concept also refined the role of T cells in the intermediate diseases (that is, those diseases that are classed as intermediates between autoimmunity and autoinflammation). Within the spondyloarthritis spectrum, this intermediate family of diseases is linked to two cytokines other than IL-1 that are crucial to neutrophil function, namely, IL-23 and IL-17 family members, whose biology is nuanced and incompletely defined across various spondyloarthritis domains[6].

Macrophage-activation syndrome (termed 'primary hemophagocytic lymphohistiocytosis' in the haematology setting) is linked to killing defects of natural killer cells and $CD8^+$ T cells. However, evidence indicates that macrophage-activation syndrome in Still's disease (which encompasses systemic juvenile idiopathic arthritis and adult-onset Still's disease) might be a T cell-mediated immune hypersensitivity response that manifests in a clinical manner similar to that of macrophage-activation syndrome[7].

In 2006, it seemed odd that systemic lupus erythematosus (SLE), although predominantly considered to be at the extreme autoimmune end of the spectrum, also extended to the autoinflammatory end of the spectrum[3]. Nevertheless, complement, the soluble arm of innate immunity, has been linked to SLE. Around the same time, multiple monogenic forms of SLE were being reported that resulted from dysregulated nucleic acid sensing and type I interferon signalling. This research placed innate immunity, or autoinflammatory mechanisms, as foundational in some SLE phenotypes[8]. Further research highlighted differences between IL-1 and type I interferon-related disease manifestations as either autoinflammatory disease or autoimmune SLE mechanisms[9].

Although the original autoinflammatory diseases comprised just a few members, numerous monogenic and polygenic diseases have now been described. For example, the seronegative spondyloarthritis concept is strongly linked to dysfunction of the intestinal barrier, and over 50 monogenic forms of inflammatory bowel disease have now been defined, including barrier protein disruption, cytokine pathway dysregulation and T cell dysregulation[10]. Thus, although inflammatory bowel disease sits closer to innate immunity than to adaptive immunity, there is tremendous immunological heterogeneity within a limited number of clinical phenotypes.

The introduction of the autoinflammation concept ultimately provided a 'doctrine of opposites' reconciliation of innate and adaptive immune mechanisms and solidly defined a new boundary of self-directed inflammation. Crucially, it provided a genetic blueprint for the understanding of disparate immunopathology and the foundation for innate immune therapeutics beyond colchicine – a 4,000-year-old Egyptian development. For sporadic non-hereditary inflammatory diseases in older individuals, there has been increased recognition of somatic mutations in innate immune cells that blend into the myelodysplastic syndromes in haematology.

In the contemporary era, many autoinflammatory diseases remain genetically unresolved, with environmental, epigenetic and somatic mechanisms being increasingly recognized as key contributors to disease pathogenesis[11]. However, on the basis of clinical phenotypes, the stratification of autoinflammatory diseases is possible

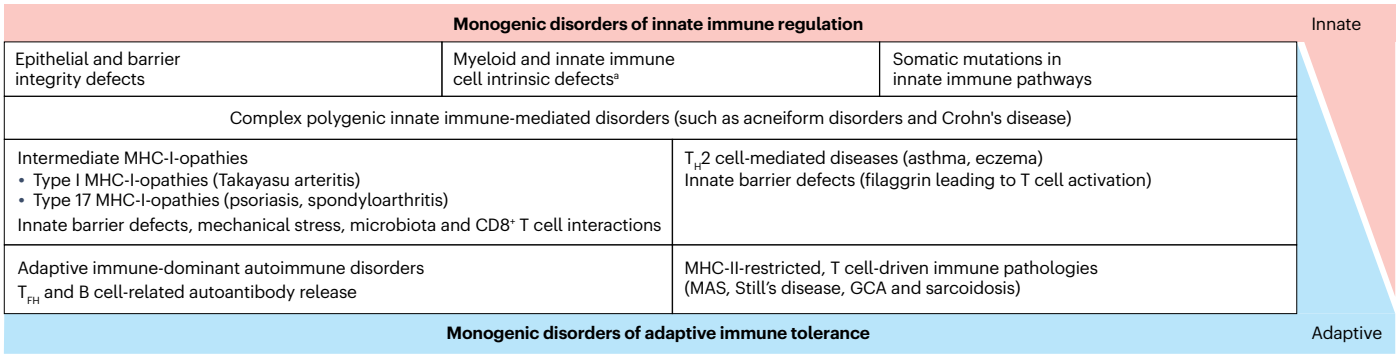

Fig. 1 | Major categories within the immunological disease continuum. The original immunological disease continuum placed monogenic innate immune diseases and adaptive immune diseases at opposite ends of the spectrum. However, in the context of autoinflammatory diseases, multiple mechanisms and multiple pathways in barrier tissues and in innate cells have been described. Somatic mutations in innate immune cells (such as in VEXAS syndrome) contribute to sporadic late-onset autoinflammatory diseases. At the autoimmune end of the spectrum, events taking place in the primary and secondary lymphoid organs lead to humoral autoantibody-mediated diseases or T cell-mediated diseases. The intermediate diseases involve abnormal barrier or tissue biomechanical stress responses that are then associated with T cell responses in the target tissues. This scenario is associated with dysregulation of the IL-23–IL-17 axis in $CD8^+$ T cells, which promotes neutrophilic pathology in the spondyloarthritis spectrum of diseases as so-called type 17 immune responses. Barrier dysfunction in the skin or lungs might likewise activate T cells in what is termed type 2 immunity, which is strongly linked to IL-4 and IL-13 dysregulation. [a]Multiple pathways, including IL-1 dysregulation in monogenic disease. GCA, giant cell arteritis; MAS, macrophage activation syndrome; T_{FH}, follicular helper T; T_H2 cell, type 2 helper T cell.

without knowledge of the underlying genetics, which brings with it empirical and novel therapeutic strategies beyond the '*horror autotoxicus*' concept (Fig. 1). Thus, the *horror autoinflammaticus* and *horror autotoxicus* concepts have been revealed to be distinct but also sometimes intertwined, and this places the future of translational immunology on a sound clinical foundation. The function of innate and adaptive immunity can be directly extended to understanding inflammation against self without an exclusive focus on the autoimmunity concept.

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Published online: 8 June 2026

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Acknowledgements

The authors thank K. Abacar for assistance with figure preparation.

Competing interests

The authors declare no competing interests.

Sjögren disease

Lytic cell death turns TRIM21 into an autoantigen

Sjögren disease is characterized by chronic inflammation and autoantibody production against intracellular antigens such as TRIM21 (also known as Ro52); however, how TRIM21 becomes an autoantigen has remained unclear. Findings now demonstrate that lytic inflammatory cell death releases TRIM21, promoting the formation of immune complexes that are taken up by macrophages and contribute to loss of immune tolerance and inflammation.

Using mouse bone marrow-derived macrophages and HeLa cells, the researchers found that TRIM21 expression is upregulated by interferons and pathogen-associated inflammatory stimuli, and that TRIM21 is released during lytic forms of cell death (such as pyroptosis and necroptosis), but not apoptosis.

"Although many proteins are released from dying cells, TRIM21 is different," explains Lynn Dustin, co-corresponding author on the study. "TRIM21 binds antibody Fc domains with very high affinity and, once released, can attach to circulating antibodies to form large immune complexes. In autoimmune diseases, these complexes increase further because anti-TRIM21 autoantibodies bind to TRIM21 through both Fc and $F(ab')_2$ regions."

The researchers found that plasma from individuals with Sjögren disease — particularly those with high anti-TRIM21 autoantibody titres — promoted the formation of large immune complexes with green fluorescent protein (GFP)-tagged TRIM21 via both Fc-mediated and $F(ab')_2$-mediated interactions in cell-free assays. When added to macrophages, these complexes were rapidly internalized via Fcγ receptor-dependent and actin-dependent pathways, with uptake efficiency increasing with immune complex size.

Once internalized, the TRIM21–IgG complexes could escape endolysosomes and enhance antigen cross-presentation, leading to increased activation of antigen-specific $CD8^+$ T cells. TRIM21 uptake also induced the production of various pro-inflammatory cytokines and metabolic responses in macrophages.

"The ability of TRIM21 immune complexes to activate macrophages resembles the biology of other cytosolic autoantigens, which usually get released as part of DNA complexes or neutrophil extracellular traps," says Dustin. "These large complexes are also taken up by macrophages, which activate macrophage innate receptors and perpetuate inflammation."

"This study uncovers an important aspect of biology and sheds light on why and how some amongst many cytosolic proteins become autoantigens," adds co-corresponding author Jelena Bezbradica. "We now need to understand where extracellular TRIM21 complexes are formed in vivo and how TRIM21 autoantibodies synergize with other autoantibodies and other immunogens to perpetuate antigen processing, macrophage activation, and inflammation."

Jessica McHugh

Original article: Jones Evans, E. L. et al. The autoantigen TRIM21 assembles proinflammatory immune complexes after lytic cell death. *Sci. Immunol.* **11**, eads9680 (2026)

Autoimmunity

Type I interferon mediates autoimmune photosensitivity

Cutaneous lupus erythematosus (CLE) and dermatomyositis are photosensitive diseases, in which ultraviolet (UV) light causes inflammation, but the underlying mechanisms that mediate this process remain unclear. Now, findings published in *Nature Immunology* provide insights into the link between UV exposure and skin inflammation.

The co-corresponding author of this article Mehdi Rashighi explains the study rationale: "Our prior work, together with studies from others in inflammatory skin disease, suggested that clinically normal-appearing, non-lesional skin is not necessarily immunologically normal … which raised an important conceptual question … could clinically unaffected skin in patients with CLE or dermatomyositis already be primed to respond abnormally to environmental triggers such as UV radiation?"

To address this question, the authors analysed lesional and non-lesional skin from people with photoresponsive (psoriasis and vitiligo) and photosensitive disease (CLE and dermatomyositis). A type I interferon signature was observed in both lesional and non-lesional photosensitive skin, but not in photoresponsive skin. Keratinocytes in both lesional and non-lesional photosensitive skin had a type I interferon signature, indicating interferon sensitization. Upon UV exposure, these keratinocytes released pro-inflammatory mediators (IL-6, IL-1 and TNF), which activate skin fibroblasts.

The researchers identified a subset of $MMP9^+CD14^+$ myeloid cells that accumulated at the dermal–epidermal junction in photosensitive skin and produced IFNβ. These myeloid cells were recruited in response to chemokines released by activated fibroblasts. Once in the tissue, these cells acquired a pro-inflammatory phenotype and promoted tissue invasiveness and inflammation. $MMP9^+CD14^+$ myeloid cells were found in close proximity to cytotoxic $CD4^+$ T cells. In vitro stimulation of $CD4^+$ T cells with IFNβ increased granzyme B expression and cytotoxicity, showing that an interferon-mediated cascade promotes skin inflammation in these photosensitive diseases.

The authors next conducted an in vivo proof-of-concept photoprovocation study in people with dermatomyositis and healthy individuals. UV irradiation induced a robust influx of $CD14^+$ cells into non-lesional dermatomyositis skin within 24 hours. In a patient with CLE treated with three monthly infusions of anifrolumab (anti-IFNAR drug), UV exposure before treatment led to a similar cell influx in non-lesional skin, but not after treatment.

"As MMP9 inhibitors have already undergone clinical safety testing in other settings, this pathway could represent a plausible future therapeutic strategy to reduce photosensitivity and inflammatory flares," Rashighi comments.

Holly Webster

Original article: Wang, Y. et al. A spatially coordinated keratinocyte–fibroblast circuit recruits $MMP9^+$ myeloid cells to drive type I interferon-driven inflammation in photosensitive autoimmunity. *Nat. Immunol.* https://doi.org/10.1038/s41590-026-02502-w (2026)

Systemic sclerosis

Anti-CD19 CAR T cell therapy promotes skin remodelling in systemic sclerosis

Reversing fibrosis in systemic sclerosis (SSc), and in other fibrotic diseases, represents a substantial clinical challenge. Now, findings indicate that anti-CD19 chimeric antigen receptor (CAR) T cell therapy, which induces deep B cell depletion, can promote regeneration of fibrotic skin tissue in SSc.

In this proof-of-concept study, the authors analysed sequential biopsy-obtained skin samples from 11 people with diffuse cutaneous SSc before anti-CD19 CAR T cell therapy and 1, 6 and 12 months after treatment. Skin samples from a patient receiving standard of care treatment and a patient with diffuse cutaneous SSc whose disease stabilized following standard of care therapy were included as exploratory controls.

As expected, peripheral B cells were completely depleted 9 days after anti-CD19 CAR T cell treatment. Tissue B cells were absent from skin samples, and serum anti-Scl70 autoantibodies were detected at all time points, but titres declined over time. Bulk RNA sequencing of skin samples revealed that B cell activation and signalling pathways were downregulated.

Histological analyses showed an increase in the number and height of dermal papillae, improvement in skin architecture and fibrosis regression (based on reduced collagen fibre alignment), changes that were not observed in control skin samples. These histological changes were reflected clinically; the modified Rodnan skin score was reduced at 1, 6 and 12 months, alongside improvements in Raynaud phenomenon.

At both transcriptomic and protein levels, fibroblast populations were altered following CAR T cell therapy: pro-fibrotic myofibroblasts and pro-inflammatory fibroblasts were diminished, and fibroblast subsets associated with homeostasis expanded. These effects were particularly prominent in the papillary layer. Genes associated with fibrosis were downregulated and those associated with regeneration were upregulated, indicative of a functional shift in fibroblasts after CAR T cell therapy.

Treatment also improved skin vasculature. Capillary density increased at 6 and 12 months, vessel structure and perfusion improved, and pro-angiogenic pathways were upregulated. Epidermal remodelling also occurred, characterized by an increase in rete ridges (indicative of epidermal regeneration) and upregulation of gene signatures associated with epidermal development and differentiation and cell signalling pathways associated with repair.

Taken together, these results indicate that deep B cell depletion via anti-CD19 CAR T cell therapy can induce fibrotic skin regeneration in SSc by reshaping fibroblast subsets and function and restoring vascular and epidermal structure.

Holly Webster

Original article: Rius Rigau, A. et al. Deep phenotyping of skin tissue remodeling in patients with systemic sclerosis treated with CD19-CAR T cells. *Nat. Commun.* **17**, 4650 (2026)

Related article: Distler, J. H. W. et al. Mechanisms of fibrotic tissue remodelling: insights from systemic sclerosis. *Nat. Rev. Rheumatol.* **22**, 221–238 (2026)

Osteoarthritis

https://doi.org/10.1038/s41584-026-01389-z

Rethinking early-stage knee osteoarthritis beyond radiography

Armaghan Mahmoudian & Ida K. Haugen

Symptomatic knee osteoarthritis at an early structural stage could provide a window of opportunity for intervention. Symptomatic knees without definite radiographic osteoarthritis can already show structural joint changes detectable on MRI; however, the greater sensitivity of MRI must be balanced against the risks of overdiagnosis and overtreatment.

Refers to Drummen, S. J. J. et al. The associations between a diagnosis of early-stage knee osteoarthritis and the presence of MRI abnormalities in knees without radiographic osteoarthritis: data from 1513 knees of the osteoarthritis initiative. *Osteoarthritis Cartilage* https://doi.org/10.1016/j.joca.2026.02.015 (2026).

Early-stage knee osteoarthritis (OA) remains clinically challenging to define. Interventions aimed at slowing or modifying disease progression are most likely to succeed before substantial structural damage has accumulated, yet consensus on how to identify clinically meaningful early-stage disease remains elusive. Conventional radiography lacks sensitivity to early pathological changes, whereas more sensitive imaging modalities raise concerns about overdiagnosis. In this context, Drummen et al.[1] asked whether symptomatic knees without definite radiographic OA already show structural abnormalities consistent with early-stage disease, providing timely insight into current efforts to define knee OA at an early structural stage.

Early-stage knee OA lacks validated definitions. A scoping review in 2023 showed that published definitions vary widely[2], and many so-called early knee OA studies still include knees with Kellgren–Lawrence grade 2 or higher, representing established structural disease rather than truly early disease stages[2]. Such heterogeneity complicates comparison across studies and interpretation of findings, and highlights the ongoing challenge of defining knee OA at the early stages in both research and clinical contexts.

The CREDO (Criteria for the Early Diagnosis of Osteoarthritis) project has developed diagnostic models to identify early-stage knee OA on the basis of demographics, symptoms and findings on clinical examination[1]. This work aligns with the ongoing Osteoarthritis Research Society International (OARSI) initiative on symptomatic knee OA at an early structural stage (EsSKOA), which focuses on developing classification criteria for research[3]. Together, these two initiatives address complementary needs: clinical diagnosis and classification for research. Diagnostic tools aim to help clinicians in identifying probable disease in individual patients and therefore require adequate sensitivity, whereas classification criteria are designed to define more homogeneous groups for research settings and typically prioritize specificity[4]. Both efforts share the objective of enabling earlier identification of knee OA and overcoming limitations of current criteria, which tend to bias towards more advanced disease.

Achieving this shift requires moving beyond the notion that OA begins only once radiographs of the joint become clearly abnormal. Heavy reliance on radiographic grading has well-recognized limitations: Kellgren–Lawrence grades compress heterogeneous joint states into a single ordinal score. Even within the same Kellgren–Lawrence category, knees can show widely different combinations of cartilage damage and osteophyte burden on MRI[5]. A normal or near-normal radiograph therefore does not equate to structural normality.

Drummen et al.[1] reinforce this point from a clinical perspective by posing a practical question: when a patient presents with knee symptoms but has normal or near-normal radiographs, does structural joint involvement already exist? The analysis suggests such involvement is common, as application of the CREDO criteria identified a subgroup with a higher prevalence of MRI abnormalities despite the absence of definite radiographic OA[1]. This observation aligns with the concept of knee OA as a continuum, in which molecular, structural and symptomatic changes evolve over time within the same joint, although not necessarily in synchrony or at the same rate.

The most obvious differences between early-stage knee OA and no knee OA involved bone marrow lesions (BMLs) and meniscal extrusion. These findings carry clear clinical relevance. Both features have been linked to structural progression and cartilage loss[6], and BMLs are among the MRI features most strongly linked to pain[7]. Thus, these observations indicate that the MRI features reported by Drummen et al.[1] are not simply incidental structural findings, but instead represent abnormalities consistently associated with symptom burden and subsequent structural worsening.

The study also highlights the challenge of specificity. MRI abnormalities were also common in knees without clinically defined knee OA. For example, cartilage defects were present in 58.6% of knees not classified as early-stage knee OA. Such findings mirror analyses from the Framingham OA Study, which demonstrated a high frequency of MRI abnormalities in radiographically normal knees[8]. Hence, MRI findings alone cannot be used to classify or diagnose OA. Existing MRI-based definitions of OA, despite being more sensitive to pre-radiographic changes, do not reliably identify knees that later develop clinically meaningful disease[9]. Consistent with this limitation, comparisons of early OA definitions in longitudinal cohorts show that many knees classified as early OA remain stable over two to five years, complicating efforts to enrich prevention trials[10].

From a clinical perspective, another important message is that not every structural change on MRI warrants an OA label in an individual patient. In people with absent or minimal symptoms, such findings might be better described as age-related structural changes or as

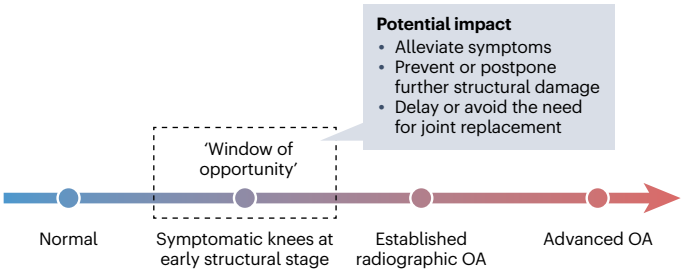

Fig. 1 | Continuum of knee osteoarthritis and the potential window of opportunity. Knee osteoarthritis (OA) progresses from early symptomatic disease with limited structural changes to advanced stages characterized by irreversible joint changes. Within the CREDO (Criteria for the Early Diagnosis of Osteoarthritis) framework, the early structural stage is recognized as a potential 'window of opportunity' during which timely recognition and intervention targeting modifiable factors could alleviate symptoms, slow structural progression and delay or avoid the need for joint replacement.

markers of increased risk rather than disease. This distinction has practical consequences for patient communication and decision-making, helping to limit overdiagnosis, overtreatment and unnecessary concern.

Valid diagnostic criteria for early-stage knee OA could have important clinical implications, but not because they would replace radiography with MRI. Current national guidelines, including those from NICE in the UK and the Swedish National Board of Health and Welfare, already make clear that routine radiography, and certainly MRI, is not needed for the diagnosis of typical OA in clinical practice. Instead, the value of early-stage knee OA diagnostic criteria lies in supporting more consistent recognition of symptomatic patients who might represent a clinically meaningful early-stage disease state within the broader spectrum of knee pain. Such recognition could support timely use of interventions such as exercise therapy, weight management if needed, patient education and appropriate follow-up, without requiring definite radiographic OA. Communication around early-stage disease must nevertheless remain proportionate: not every MRI abnormality represents disease, not every structural change warrants an OA label and not every knee with symptoms will progress to established OA.

The study by Drummen et al.[1] supports the view that structural abnormalities can already be present before becoming apparent on radiographs, and that diagnostic tools incorporating demographics, symptoms and findings on clinical examination can help identify such knees. The CREDO project aligns well with the ongoing maturation of the field, which increasingly focuses on knee OA at an early structural stage, a phase that might represent a 'window of opportunity' to alleviate symptoms and to potentially delay or prevent further structural damage (Fig. 1), as well as the establishment of chronic pain states and maladaptive biomechanical changes.

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Published online: 27 May 2026

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Acknowledgements

We thank L. S. Lohmander for his thoughtful and constructive feedback, which helped to sharpen the conceptual framing and clinical relevance of this piece.

Competing interests

A.M. has received personal fees from Novo Nordisk outside the submitted work. I.K.H. has received personal fees from Argenx, Pacira, Grünenthal and AbbVie outside the submitted work.

nature reviews rheumatology

https://doi.org/10.1038/s41584-026-01379-1

Review article

Check for updates

Treatment strategies in giant cell arteritis and polymyalgia rheumatica: beyond glucocorticoids

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Abstract

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are closely related chronic inflammatory conditions. Glucocorticoids remain the cornerstone of treatment for both conditions, as they rapidly control inflammation and also reduce the risk of ischaemic complications in GCA. However, glucocorticoid therapy is often prolonged and associated with substantial treatment-related morbidity. In addition, many patients experience relapses during glucocorticoid maintenance therapy and can accrue vascular damage. Advances in understanding the immunopathology of GCA and PMR have led to the development of targeted therapies, particularly agents inhibiting the IL-6 pathway and, more recently, Janus kinase (JAK) signalling. IL-6 receptor inhibitors reduce the risk of disease relapse and allow for reduction in glucocorticoid use in both GCA and PMR, and JAK inhibition enables glucocorticoid sparing and lowers the risk of relapse in GCA. Optimal management of GCA and PMR requires close monitoring, careful assessment of disease activity and treatment-related toxicity, as well as individualized therapeutic strategies. Ongoing research continues to refine treatment algorithms and could help to define therapeutic targets across GCA and PMR. Emerging therapeutic options and evolving treatment algorithms reflect the dynamic and patient-centred nature of advancements in GCA and PMR management.

Sections

Introduction

Giant cell arteritis

Polymyalgia rheumatica

Future perspectives for giant cell arteritis and polymyalgia rheumatica treatment

Conclusions

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Key points

- Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are closely related inflammatory disorders for which glucocorticoids remain the cornerstone of treatment, but new advances are improving treatment strategies for both conditions.
- Glucocorticoids rapidly control inflammation in GCA and PMR and reduce ischaemic risk in GCA but are associated with substantial treatment-related morbidity that can impair patients' quality of life.
- Relapses are common in both diseases and contribute to prolonged exposure to glucocorticoids.
- IL-6 receptor inhibitors reduce relapse risk and cumulative glucocorticoid exposure in both GCA and PMR, and Janus kinase (JAK) inhibitors reduce the risk of relapse and glucocorticoid use in GCA.
- Future management strategies will likely integrate targeted therapies with improved monitoring of disease activity in GCA and PMR.

Introduction

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are among the most common inflammatory rheumatic diseases in older adults[1]. Although traditionally considered distinct clinical entities, substantial clinical, epidemiological and pathogenic overlap has led to the view that they represent manifestations along a shared disease continuum[2].

The close relationship between these conditions has been recognized for decades[3]. Early clinical descriptions emphasized their frequent coexistence, and in 1964 Hamrin et al.[4] proposed the term 'polymyalgia arteritica' to highlight the link between polymyalgic symptoms and underlying arteritis. This close relationship is supported by several observations. Up to half of patients with GCA experience symptoms of PMR, and subclinical large-vessel vasculitis can be detected in a substantial proportion of patients with apparently isolated PMR[1,5]. These findings suggest that systemic inflammation, musculoskeletal manifestations and vascular involvement can occur together in GCA and PMR.

Glucocorticoids remain the cornerstone of treatment for both conditions and rapidly control systemic inflammation. However, relapses are frequent, and many patients require prolonged glucocorticoid therapy, exposing them to substantial treatment-related morbidity. These limitations have stimulated increasing interest in glucocorticoid-sparing strategies and in the development of novel therapies. Advances in the understanding of the immunopathology of GCA and PMR, particularly the role of IL-6 signalling and other inflammatory pathways, have led to the emergence of biologic and targeted synthetic therapies. These developments are reshaping treatment strategies and raising new questions regarding optimal treatment sequencing and duration, monitoring of disease activity and long-term management.

Conceptual frameworks such as treat-to-target (T2T) have been proposed to guide the management of chronic inflammatory diseases[6,7] (Box 1). In GCA and PMR, however, implementation of T2T remains challenging owing to the lack of validated definitions of remission and reliable biomarkers of disease activity[8–12]. Nevertheless, the principles of defining therapeutic goals, monitoring disease activity and minimizing treatment-related toxicity remain highly relevant in clinical practice.

In this Review, we discuss current therapeutic strategies for GCA and PMR. Although these conditions are increasingly viewed as manifestations of a shared GCA–PMR disease spectrum, most clinical trials and therapeutic studies have evaluated them separately. Accordingly, we present treatment strategies for GCA and PMR in distinct sections. This approach reflects the substantial differences in disease severity, risk of permanent damage (vascular in GCA), treatment goals, and the strength of the available evidence for clinical management of GCA and PMR. Our aim is to provide a clear, clinically oriented overview of current therapeutic options for each condition while highlighting areas of overlap in pathophysiology and clinical presentation. We summarize evidence supporting glucocorticoid therapy, examine emerging glucocorticoid-sparing approaches including biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), and discuss challenges in monitoring disease activity and defining treatment targets. Finally, we highlight key unresolved questions and future directions for the management of the GCA–PMR disease spectrum.

Giant cell arteritis

General principles of giant cell arteritis treatment

In GCA, the primary objective of treatment is to alleviate patient symptoms and decrease the risk of damage due to vasculitis, particularly ischaemic optic neuropathy and cerebrovascular events. A suggested treatment algorithm for GCA is provided in Fig. 1.

Initial treatment with glucocorticoids in patients with and without severe ischaemic events. Glucocorticoids remain an essential therapy for remission induction in GCA, demonstrating high efficacy in rapidly suppressing disease signs and symptoms. Moreover, early retrospective studies comparing outcomes in glucocorticoid-treated patients with those in patients treated prior to the introduction of glucocorticoids indicated that cortisone was associated with a reduction in the incidence of vision loss[3,13]. Owing to the potential for ischaemic events, glucocorticoid therapy should be initiated promptly in people with a high clinical likelihood of GCA while confirmation of the diagnosis is underway.

The treatment of choice is oral prednisone (or its equivalent) at an initial dose of 40–60 mg daily for 1–2 weeks, followed by gradual tapering. Although guidelines uniformly recommend early treatment with high-dose glucocorticoid regimens, the optimal starting dose has not been formally evaluated in randomized clinical trials (RCTs)[14,15]. Interestingly, in a retrospective study, it was noted that patients treated with an initial oral prednisone dose >40 mg per day achieved earlier prednisone discontinuation than patients who received ≤40 mg per day initially[16]. The tapering schedule that follows high-dose glucocorticoid treatment is highly variable and depends on patient characteristics, response to therapy and use of glucocorticoid-sparing agents. Alternate-day glucocorticoid therapy is not advised: randomized, prospective studies have demonstrated that disease control is inadequate with alternate-day regimens compared with daily dosing[14].

The role of glucocorticoid pulse therapy. For patients who present with impending or recent visual loss, induction therapy with intravenous pulse methylprednisolone (250–1,000 mg daily for 3 days) is recommended, followed by oral prednisone (or its equivalent) at an initial dose of 40–60 mg daily[14,15]. Retrospective data indicate that patients with visual impairment who received intravenous glucocorticoids were more likely to experience improvement than those treated with oral glucocorticoids alone[17]. However, the advantage of intravenous pulse

glucocorticoids over oral therapy remains debated, as established ischaemic optic neuropathy is frequently irreversible and other studies have not shown benefit for improving visual acuity[18]. Moreover, pulse glucocorticoid therapy is associated with an increased risk of adverse effects in older adults with GCA, particularly symptoms such as anxiety, insomnia and agitation[19].

Initial intravenous bolus administration of methylprednisolone, followed by oral glucocorticoids tapered by reducing the daily dose every 2 weeks (40 mg, 30 mg, 25 mg, 20 mg, 17.5 mg, 15 mg, 12.5 mg, 10 mg, then 1-mg decrements), can reduce long-term glucocorticoid requirements according to one trial, although another study showed that pulse methylprednisolone does not modify the disease course nor does it provide glucocorticoid-sparing effects[20,21]. At present, pulse-dose glucocorticoids are not recommended in patients without ischaemic complications.

Traditional immunosuppressants as glucocorticoid-sparing agents. Glucocorticoid-sparing medications should be considered for all patients with GCA, particularly those at risk of, or with ongoing, glucocorticoid-related toxicity. Methotrexate is the conventional immunosuppressive agent that has undergone the most rigorous evaluation for the management of GCA. RCTs evaluating the efficacy of methotrexate yielded conflicting results. A meta-analysis[22] of three randomized placebo-controlled trials suggested that therapy with low-dose methotrexate (7.5–20 mg) enables a reduction in prednisone dosage while reducing the risk of a first GCA relapse by 35% and of a second relapse by 51%. However, a decrease in glucocorticoid-related toxicity was not observed in this analysis and clinicians should be aware of a delay (approximately 6 months) before a therapeutic effect of methotrexate becomes apparent[22]. Although of modest efficacy, methotrexate can be considered as an alternative to tocilizumab or upadacitinib (which are discussed in more detail later in this Review). Specifically, methotrexate can be used in the treatment of patients who have limited access, contraindications or intolerance to tocilizumab or upadacitinib. American College of Rheumatology–Vasculitis Foundation (ACR–VF) and European Alliance of Associations for Rheumatology (EULAR) guidelines endorse the use of methotrexate as an alternative to tocilizumab[14,15]. The METOGiA trial (published to date only as an abstract[23]) was an open-label, randomized, non-inferiority study that compared methotrexate with tocilizumab, each combined with a standardized glucocorticoid taper, in patients with new-onset or relapsing GCA. At week 78, methotrexate was not non-inferior to tocilizumab with respect to the primary end point (survival without relapse or deviation from the glucocorticoid taper) and secondary outcomes suggested that tocilizumab had greater efficacy[23]. However, publication of the full trial methodology and results is awaited.

Data on the use of other conventional immunosuppressive medications for GCA are limited, of low quality or negative. Azathioprine has been evaluated in a placebo-controlled trial and was found to be of limited benefit[24]. Cyclosporin does not seem to have a role in the treatment of GCA[25]. Use of dapsone and hydroxychloroquine has been reported, but these agents have not been studied in RCTs and are not recommended[26,27]. An open-label clinical trial demonstrated that leflunomide could have a glucocorticoid-sparing effect in GCA, although in clinical practice its use is infrequent and is limited to patients who have failed to respond to more effective therapies[28]. Owing to its toxicity, cyclophosphamide is only used in exceptional circumstances for patients with life-threatening disease (for example, intracranial vasculitis) that is refractory to standard therapy[29].

Box 1 | Treat-to-target in giant cell arteritis and polymyalgia rheumatica

Treat to target (T2T) is a management strategy for chronic diseases that involves defining a therapeutic target, regularly assessing disease activity and adjusting treatment when the target is not achieved[6]. In giant cell arteritis (GCA) and polymyalgia rheumatica (PMR), the proposed treatment goal is the achievement and maintenance of remission while minimizing treatment-related adverse events and preserving health-related quality of life[7]. However, implementation of T2T in these diseases remains challenging.

A universally accepted definition of remission is lacking, and commonly used biomarkers of systemic inflammation, such as acute-phase reactants, can be unreliable in patients treated with IL-6 pathway inhibitors[8–12]. In clinical practice, remission is therefore generally defined by the absence of disease-related clinical manifestations, together with normalization of inflammatory markers[7].

Regular monitoring is recommended, particularly during glucocorticoid tapering, when relapses most commonly occur[7]. Future studies aimed at identifying reliable biomarkers and imaging parameters of disease activity could facilitate the implementation of T2T strategies in PMR and GCA. Assessment of vascular damage progression should also be considered when making clinical decisions, as it might influence treatment intensity, monitoring frequency and long-term management strategies.

The role of antiplatelet and anticoagulant therapies. The efficacy of aspirin to prevent ischaemic events in patients with GCA remains unclear. Observational studies have suggested that rates of visual loss and cerebrovascular events are lower in people being treated with aspirin, although other studies have not confirmed a consistent benefit of antiplatelet therapy[30–32]. No RCTs have assessed the safety and efficacy of aspirin as an adjunctive treatment in GCA[33]. EULAR guidelines discourage the routine use of antiplatelet therapy for GCA, recommending its prescription only to patients with cardiovascular or cerebrovascular indications[15]. ACR–VF guidelines recommend the use of aspirin for patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries[14]. A 2025 retrospective study of nearly 2,000 patients with GCA found that those on anticoagulants prior to GCA diagnosis had a reduced risk of cranial ischaemic events, whereas a protective effect was not seen with anti-platelet therapy[34].

Glucocorticoid-sparing agents

Pathophysiological rationale for the development of new treatment in giant cell arteritis. A pathophysiological rationale for the development of new treatments in GCA is presented in Fig. 2. Inflamed arteries in people with GCA are characterized by infiltrating immune cells, mainly macrophages and $CD4^+$ T lymphocytes, as well as by tissue remodelling. Functional studies using human artery–mouse chimaera models, ex vivo culture of samples obtained via temporal artery biopsy (TAB), and primary TAB-derived cultures indicate roles for T cells, dendritic cells (DCs), monocyte–macrophages and possibly B cells and fibroblasts in GCA pathogenesis. Cytokines, growth factors, receptors and other molecules involved in GCA pathogenesis include TLR4, CCR7,

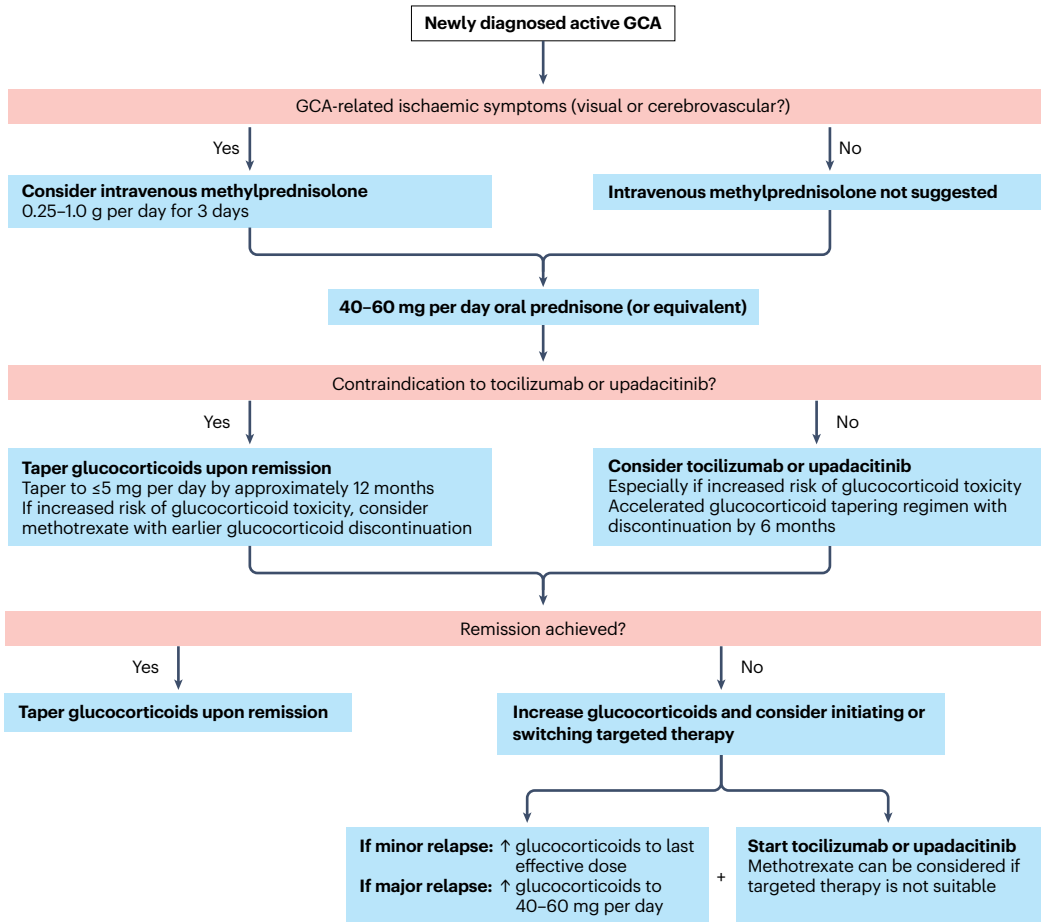

Fig. 1 | Treatment algorithm for giant cell arteritis. This algorithm summarizes a pragmatic approach to the management of patients with giant cell arteritis (GCA). Glucocorticoids remain the cornerstone of remission induction. In patients presenting with visual or cerebrovascular ischaemic manifestations, intravenous methylprednisolone can be considered before initiation of high-dose oral glucocorticoid therapy. Targeted therapies such as tocilizumab or upadacitinib can be considered early in the disease course, particularly in patients with relapsing or refractory disease or in those at an increased risk of glucocorticoid-related adverse effects. Methotrexate can be considered as an alternative glucocorticoid-sparing agent when targeted therapies are contraindicated or not suitable. Treatment should be guided by regular assessment of disease activity. In patients who do not achieve disease control, escalation of glucocorticoid therapy and initiation or modification of targeted therapy can be considered. Minor relapses can be managed by increasing the glucocorticoid dose to the last effective dose, whereas major relapses usually require higher glucocorticoid doses. Once remission is achieved, gradual tapering of glucocorticoids is recommended. In patients receiving glucocorticoid-sparing therapies, faster tapering and earlier discontinuation of glucocorticoids could be feasible. In patients in a state of sustained remission receiving combination therapy, glucocorticoids are typically tapered first, whereas targeted or conventional immunomodulatory therapies are usually maintained longer before dose reduction or discontinuation is considered.

CCR6, MMP9, Janus kinases (JAKs), Notch–Jagged, vascular endothelial growth factor, IL-6, IL-9, IL-12–IL-23, IL-17, IL-22, IFNγ, GM-CSF, GM-CSFR, CD96–CD155, PD1–PDL1, endothelin 1, serum amyloid A, PDGF and miR-146a/b[35–38].

The current model of GCA pathogenesis identifies adventitial DCs as contributors to disease initiation, acting in concert with autoreactive T cells[39]. DCs are activated by unknown stimuli, display defects in inhibitory immune checkpoints and persist within the arterial wall[40,41]. Activated DCs produce chemokines that recruit lymphocytes and monocytes to the arteries from the circulation and secrete interleukins that drive lymphocyte differentiation. High-throughput transcriptomic studies of TAB-obtained specimens from patients with GCA have confirmed that the expression of multiple chemokine-coding genes is elevated in temporal artery tissues[42].

Multiple T helper subsets, namely T_H1 cells, T_H9 cells, T_H17 cells, T_H21 cells and T_H22 cells, are found within arterial lesions in GCA[43]. These cells produce cytokines that activate macrophages. Inhibiting T cell activation (for example, by using abatacept) or targeting DC stimulatory pathways could offer therapeutic benefit in GCA[39,44]. Several macrophage subtypes are present in temporal artery tissues, and produce metalloproteinases, elastases and reactive oxygen species, which contribute to tissue damage, including disruption of the internal and external elastic laminae[45,46]. Giant cells are present in approximately half of samples obtained by TAB[47]. Additionally, $CD8^+$ cytotoxic T cells and neutrophil extracellular traps seem to contribute to GCA pathogenesis[48,49].

The role of B lymphocytes in GCA remains incompletely understood. B cells can function as antigen-presenting cells and can

contribute to the local cytokine milieu, which shapes fibroblast and smooth-muscle cell phenotypes[50]. However, the presence of B cells in temporal arteries seems to be heterogeneous, with tertiary lymphoid organs in arteries identified only in a subset of patients[51]. GCA-associated autoantibodies have also been detected in sera from patients with GCA, although their occurrence is controversial and their pathogenic relevance remains unclear[52].

Tissue remodelling in GCA is characterized by a shift in the phenotype of smooth-muscle cells from a contractile to a synthetic one, phenotypic diversity among fibroblasts, myofibroblast differentiation and proliferation, intima hyperplasia and neoangiogenesis[53,54]. These processes contribute to intimal thickening and subsequent vascular stenosis, and present potential therapeutic targets, providing the basis for the development of novel treatments aimed at modulating vascular remodelling and preventing luminal occlusion.

Cells expressing senescence markers, mainly fibroblasts, macrophages and endothelial cells, are detected within arterial lesions. IL-6, along with other soluble factors present in TAB-obtained samples, seems to contribute to the local ageing process[55]; therapies targeting IL-6 are discussed in the next section.

Many cytokines recognize JAK-associated receptors and amplify the pro-inflammatory cascade through activation of the JAK–STAT signalling pathway, which provides a rationale for the use of JAK inhibitors (such as upadacitinib and baricitinib) in GCA therapy[56]. Several cytokines targeted by bDMARDs, such as IL-1β, IL-17, IL-12, IL-23, GM-CSF, G-CSF and M-CSF, are overexpressed in inflamed temporal arteries and have confirmed or potential roles in GCA pathogenesis[57–60].

Overall, therapeutic strategies that target both immune and stromal cells could offer the greatest benefit in GCA.

Efficacy and safety of tocilizumab and other IL-6 pathway inhibitors. IL-6 pathway inhibition, particularly with tocilizumab, which blocks the IL-6 receptor (IL-6R), represents the most extensively investigated biologic therapy approach in GCA, demonstrating robust efficacy in lowering relapse rates and enabling significant GC sparing.

Tocilizumab received approval from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the UK National Institute of Health and Care Excellence in 2017–2018 on the basis of two landmark clinical trials. The first RCT to demonstrate the efficacy of tocilizumab in patients with GCA was a single-centre phase II trial that included 30 patients with new-onset or relapsing GCA who were randomly allocated (2:1) to receive treatment with intravenous tocilizumab (8 mg/kg) every 4 weeks for 52 weeks plus prednisolone or placebo plus prednisolone[61]. At week 12, remission (defined as no clinical signs or symptoms of GCA and normalized erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level at a prednisolone dose of 0.1 mg/kg per day) was achieved in 85% of the tocilizumab group versus 40% of the placebo group. By week 52,

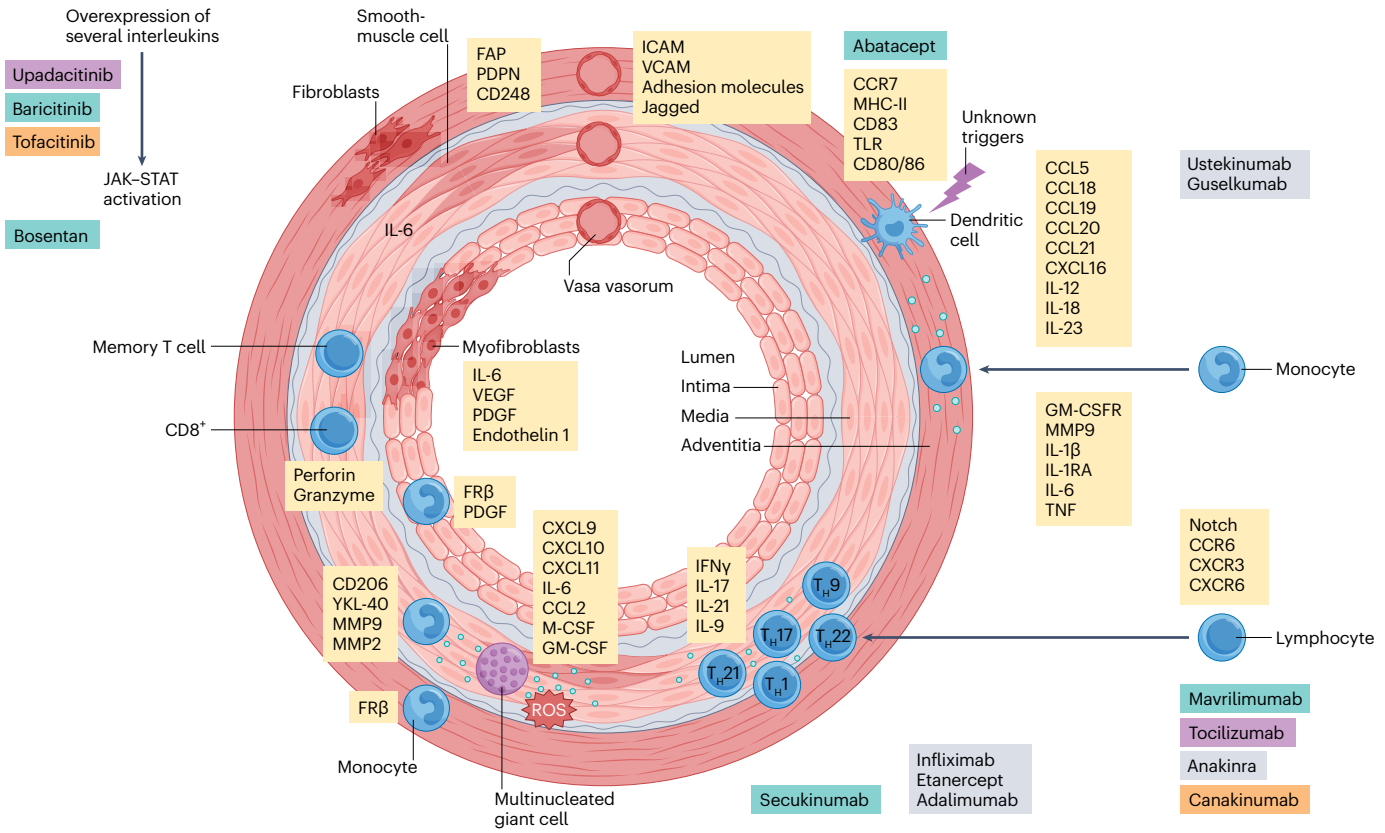

Fig. 2 | Pathophysiological rationale for the development of new treatments in giant cell arteritis. The main contributors to the pathogenesis of giant cell arteritis (GCA) are shown, as well as respective therapies. Boxes filled in violet indicate the approved drugs. Boxes filled in green indicate the drugs under study. Boxes filled in orange indicate the theoretical drugs. Grey boxes indicate the drugs that failed or that had limited activity. JAK, Janus kinase; ROS, reactive oxygen species; T_H1, T helper 1.

the rate of relapse-free survival was 85% in the tocilizumab group versus 20% in the placebo group, with significantly lower cumulative glucocorticoid exposure in the tocilizumab group[61]. These results were confirmed by the pivotal phase III GiACTA trial[62], in which 251 patients with new-onset or relapsing GCA were randomly allocated (2:1:1:1) to receive subcutaneous tocilizumab 162 mg weekly or every other week combined with a 26-week prednisone taper, or placebo combined with a 26-week or 52-week prednisone taper. The primary end point, sustained glucocorticoid-free remission at week 52, was achieved by 56% of the weekly and 53% of the every-other-week tocilizumab groups, compared with 14% and 18% of the respective placebo groups. Tocilizumab therapy markedly reduced cumulative prednisone exposure (1,862 mg in each of the tocilizumab arms versus 3,296–3,818 mg in the placebo arms). The treatment was well tolerated, with no unexpected safety signals; serious adverse events, mainly infections, were more frequent in the placebo groups[62]. Furthermore, the weekly tocilizumab regimen significantly improved SF-36 and FACIT-Fatigue scores compared with prednisone alone and restored health-related quality of life to age-matched and gender-matched normative levels by week 52 (refs. 62,63). However, tocilizumab treatment is associated with increased circulating levels of cholesterol and triglycerides and is relatively contraindicated in patients with a history of diverticulitis owing to an elevated risk of bowel perforation[64].

Long-term extensions of these phase II and phase III RCTs and real-world studies demonstrated that discontinuation of tocilizumab was followed by relapse in ~50% of patients within 1 year, indicating that long-term remission is not induced in the majority of patients, particularly those with large-vessel involvement[65–68]. Nevertheless, glucocorticoid-sparing effects persisted over 3 years, with cumulative prednisone doses being significantly lower in patients initially treated with tocilizumab compared with placebo. Restarting tocilizumab, with or without glucocorticoids, was generally effective in re-establishing remission in patients with a relapse off-treatment[66]. Collectively, clinical trials and real-world studies have shown the clinical benefit of tocilizumab irrespective of GCA phenotype, with reductions in relapse rates from ~40% to ~20%[68–70].

Despite these advances, uncertainties remain. Whether tocilizumab should be discontinued abruptly or tapered gradually remains controversial. Clinical studies have shown that tapering is associated with longer relapse-free survival and fewer early relapses; however, relapse risk remains elevated after tocilizumab is ultimately discontinued regardless of the cessation method, and the optimal duration of treatment remains unclear[71,72]. Moreover, histological and imaging studies have shown persistent vascular inflammation in one-third to half of patients who achieve clinical remission with tocilizumab therapy, suggesting that suppression of CRP by tocilizumab can lead to underestimation of disease activity and that additional disease activity biomarkers are urgently required[73–77]. Furthermore, whether tocilizumab prevents long-term vascular complications such as aneurysm or stenosis is still unclear, necessitating ongoing assessments and clinical vigilance.

Tocilizumab has nevertheless significantly changed GCA management, by improving remission rates and reducing glucocorticoid burden and glucocorticoid-associated adverse events[62,78]. With increasing access to tocilizumab biosimilar drugs, the cost-effectiveness of these therapies requires further evaluation so that more patients with GCA can benefit from them.

Alternative IL-6 inhibitors have been evaluated for the management of GCA. In a phase III RCT, sirukumab, an anti-IL-6 antibody, reduced disease flares compared with placebo and had a comparable safety profile, although the study was terminated early and two sirukumab-treated patients developed visual disturbances possibly related to GCA[79]. Sirukumab was primarily developed for the treatment of rheumatoid arthritis, but despite positive phase III efficacy data, it did not receive regulatory approval for this indication owing to safety concerns and remains unapproved worldwide for any indication. A phase III RCT of the IL-6R inhibitor sarilumab for GCA was terminated during the COVID-19 pandemic owing to slow recruitment[80].

The GiACTA trial was the first to compare standardized prednisone tapering regimens in GCA, demonstrating the superiority of a 26-week glucocorticoid taper combined with tocilizumab over conventional 52-week glucocorticoid monotherapy[62]. On the basis of these findings, a 26-week taper is recommended when tocilizumab is used[15]. More recently, a proof-of-concept study involving 30 patients with newly diagnosed or relapsing GCA showed that combining tocilizumab with only 8 weeks of prednisone treatment achieved sustained remission in 77% of patients with new-onset or relapsing GCA at week 52, with no vision loss[81].

Two proof-of-concept studies evaluated the efficacy and safety of tocilizumab monotherapy after ultra-short courses of glucocorticoid treatment. In the GUSTO trial, 18 people with newly diagnosed GCA received intravenous pulses of methylprednisolone over 3 consecutive days followed by a single intravenous infusion of tocilizumab and then weekly subcutaneous tocilizumab injections; 78% of the participants achieved remission within 24 weeks and 72% remained relapse-free at 1 year. However, the effect of treatment was delayed and only 25% of the participants achieved remission by week 4, and one case of irreversible anterior ischaemic optic neuropathy occurred in the early high-risk phase[82]. In the TOPAZIO study, 18 patients with newly diagnosed or relapsing large-vessel GCA received the same 3-day intravenous methylprednisolone regimen followed by weekly subcutaneous tocilizumab injections; sustained clinical remission was achieved in 76% of these patients at 1 year, accompanied by a significant reduction of vascular inflammation on PET–CT[83].

These proof-of-concept studies suggest that tocilizumab monotherapy can induce and maintain remission in GCA, enabling substantial reduced glucocorticoid exposure, and can be considered for minor relapses. However, ultra-short glucocorticoid regimens are not standard of care and should be avoided in patients with ischaemic symptoms as it is unclear whether this approach combined with tocilizumab can prevent visual loss or cerebrovascular events.

Janus kinase inhibitors. The JAK–STAT signalling pathway is downstream of multiple interleukins (for example, IL-6), interferons (such as IFNγ) and growth factors (including colony-stimulating factors) that are known to be upregulated in GCA. The activation of the JAK–STAT signalling pathway can in turn induce transcripts involved in immune responses and inflammation, thereby establishing positive feedback loops.

In the 2025 phase III SELECT-GCA trial[84], 428 patients with newly diagnosed or relapsing GCA were randomly allocated (2:1:1) to receive treatment with the selective JAK1 inhibitor upadacitinib, at a dose of 15 mg or 7.5 mg orally once daily plus a 26-week glucocorticoid taper, or placebo plus a 52-week glucocorticoid taper. Upadacitinib at a dose of 15 mg was superior to placebo in achieving sustained remission (46.4% versus 29.0%); the 7.5 mg dose was not significantly superior to placebo (41.1%). Upadacitinib 15 mg also delayed time to disease flare, reduced cumulative glucocorticoid exposure (1,615 mg versus 2,882 mg),

and improved fatigue and quality of life in comparison with placebo. Adverse events were generally similar across the study groups, although long-term real-world data are needed to further assess safety in this older patient population[84]. On the basis of the results of the SELECT-GCA trial, upadacitinib was approved by the FDA and EMA for treatment of GCA in 2025. In the 2-year, double-blind extension of the SELECT-GCA trial (currently available only as an abstract), patients who achieved ≥24 weeks of sustained remission during the initial 1-year phase maintained remission during the extension only if upadacitinib 15 mg was continued (68.6% versus 28.6% for those switched to placebo), with no new safety signals over 2 years, suggesting that ongoing therapy might be required to prevent relapse[85].

A prospective open-label pilot study primarily designed to assess the safety of baricitinib, a JAK1–JAK2 inhibitor, in 15 patients with relapsing GCA found that baricitinib at a dose of 4 mg daily was well tolerated, with most patients able to discontinue glucocorticoids and maintain remission over 52 weeks[86]. A phase III RCT of baricitinib has not been announced to date.

Other biologic agents. Several bDMARDs have been investigated as glucocorticoid-sparing therapies in GCA, although earlier studies used slower prednisolone tapers than that used in the GiACTA trial, which might have limited their ability to demonstrate the clinical efficacy of the bDMARD being assessed. Most studies to date have focused on cytokine inhibition, with limited studies directly targeting infiltrating T cell or macrophage populations.

Although the presence of granulomatous inflammation in GCA suggests a potential role for TNF inhibition, multiple small, randomized trials with infliximab, etanercept and adalimumab demonstrated no clinical benefit of anti-TNF therapies in this disease[87–89]. Secukinumab, an IL-17A inhibitor, showed promise in the phase II TitAIN RCT[90], but an announcement by the company developing this therapy suggested that the positive outcomes were not replicated in the phase III GCAptAIN study, in which the primary end point was not met[91]. An open-label trial of ustekinumab, which inhibits the IL-12–IL-23 pathway, a prematurely discontinued phase II trial of the IL-23 inhibitor guselkumab and a phase III trial of the IL-1 receptor antagonist anakinra all showed the limited efficacy of these approaches, with high rates of treatment failure or relapse with no meaningful reduction in glucocorticoid exposure[92–94].

Mavrilimumab, a GM-CSF receptor antagonist that directly targets macrophage biology and vascular remodelling, improved outcomes in patients with GCA in a phase II RCT, reducing flares (19% versus 46%) and increasing sustained remission at week 26 (83% vs 50%) without deaths or vision loss[95]. However, no phase III RCT has been announced to date.

Abatacept, a CTLA4–Ig fusion protein that inhibits T cell co-stimulation, also prolonged relapse-free survival when administered intravenously in conjunction with prednisone in a phase II RCT, increasing median remission duration to 9.9 months versus 3.9 months for prednisone alone, with no increase in adverse events[96]. A phase III RCT of subcutaneous abatacept for GCA (NCT04474847) is currently underway.

International recommendations for the initial treatment of giant cell arteritis

Since 2018, evidence-based guidelines on the management of GCA have been released by the EULAR[15], the ACR–VF[14] and several national scientific societies[97–101]. Updates of the EULAR and British Society for Rheumatology recommendations are expected in the near future. Overall, these guidelines largely agree on how to manage GCA in clinical practice[102]. Divergence can be explained by differences in the methodology used to formulate the guidelines and in the health care systems between the USA and most European countries, as well as by differences in opinion among expert groups considering the absence of high-quality evidence.

As untreated active GCA carries a substantial risk of visual loss[103], current guidelines agree that patients with newly diagnosed active GCA should be treated with high-dose oral glucocorticoids, whereas patients with acute visual symptoms should initially receive glucocorticoids intravenously. After remission induction, the EULAR recommends tapering the glucocorticoid dose to a target dose of 15–20 mg per day within 2–3 months and to ≤5 mg per day after 1 year. In patients receiving glucocorticoid-sparing therapy, a faster glucocorticoid taper and earlier withdrawal of glucocorticoids is advised on an individual basis[15]. By contrast, the ACR–VF guideline does not recommend a target for glucocorticoid tapering but suggests that the duration of glucocorticoid treatment should be guided by the patient's preferences, as the evidence on glucocorticoid tapering regimens and duration of treatment is low[14]. The Pan American League of Associations for Rheumatology (PANLAR) guidelines for the treatment of GCA provide recommendations similar to those of the ACR–VF regarding the use of glucocorticoids for remission induction, without specifying a target for glucocorticoid tapering[104].

Type, frequency and treatment of giant cell arteritis relapse

Prospective clinical trials and observational studies have shown that 34–75% of patients with GCA relapse if treated with glucocorticoids only[103]. Furthermore, up to 30% of those receiving adjunctive tocilizumab or upadacitinib experience disease relapses, with most relapses occurring within the first 2 years after diagnosis[85,105]. Severe ischaemic events, including blindness, however, are rare once adequate glucocorticoid therapy has been initiated.

Frequent relapses, however, often require increased exposure to glucocorticoids, which contributes to treatment-related morbidity and can exacerbate vascular damage. Tocilizumab and upadacitinib effectively reduce relapse frequency, yet over half of patients relapse after discontinuation of these therapies[65–68,85]. These observations indicate that IL-6 blockade and JAK inhibition suppress inflammation and disease activity but do not fully restore immune tolerance in a substantial proportion of patients with GCA[106].

The EULAR recommends increasing the glucocorticoid dose to 40–60 mg/day in relapsing patients with cranial features or progressive vascular damage (considered a 'major relapse') or to the last effective dose in patients without cranial symptoms ('minor relapse')[15]. EULAR, ACR–VF and PANLAR guidelines recommend adjunctive treatment for patients whose disease relapses. However, the ACR–VF guidelines also recommend the use of tocilizumab in combination with glucocorticoids over glucocorticoids alone for all patients with newly diagnosed GCA[14]. By contrast, the EULAR and its national societies recommend limiting the use of adjunctive therapies in treatment-naive patients to those with the presence of, or an increased risk of, glucocorticoid-related adverse effects[15]. The ACR–VF conditionally recommends tocilizumab over methotrexate as an adjunctive therapy in GCA[14]. The EULAR suggests that methotrexate can be used as an alternative to tocilizumab but also notes that tocilizumab provides a higher degree of confidence that a clinically meaningful treatment response will be achieved[15]. PANLAR guidelines recommend tocilizumab for all patients with new-onset GCA if available, with methotrexate as an alternative option[104].

Routine monitoring of disease activity and vascular damage

Monitoring of GCA disease activity should include clinical assessment and laboratory studies; imaging can be indicated in selected patients with suspected relapse or vascular damage[91]. Clinic visits should be more frequent during the remission-induction phase, then less often once the disease is under control. Each visit should include assessment for signs and symptoms of GCA, accompanied by a thorough vascular examination. Laboratory studies generally involve inflammatory markers, complete blood count and tests to monitor potential medication toxicity, such as renal and liver function assessments. Tocilizumab suppresses CRP production by directly inhibiting IL-6 signalling and hepatic CRP synthesis, regardless of inflammatory activity. Therefore, careful clinical assessment, supplemented by imaging in selected cases, is particularly important for monitoring patients undergoing treatment with this bDMARD. The 2023 EULAR recommendations for the use of imaging in large-vessel vasculitis specify that ultrasonography, fluorodeoxyglucose-PET, or MRI can be used for the assessment of vessel abnormalities in patients with suspected relapse[107]. However, it should be noted that changes detectable on imaging often lag behind clinical and laboratory improvement.

Individuals with GCA can develop long-term aortic complications, including aneurysm and dissection. Patients with aortic inflammation at the time of disease onset seem to be particularly at risk of such complications. In a 2023 prospective study, 106 patients with GCA underwent fluorodeoxyglucose-PET and CT imaging at diagnosis and CT imaging annually during follow-up for up to 10 years. Patients with aortitis at diagnosis demonstrated a larger increase in aortic diameter and were found to be at a tenfold higher risk of developing a thoracic aortic aneurysm over time than patients without aortitis at diagnosis[108].

Retrospective studies have shown that patients with GCA are at an up to 17-fold increased risk of thoracic aortic aneurysm compared with the general population[109,110]. However, reliable predictors of aortic aneurysm development are still lacking. Up to one-third of patients developed an aortic aneurysm within 10 years in the pre-biologic era[109,110], and one study found a 19% incidence at 15 years in the post-biologic era, a 13.5-fold increase in patients with GCA versus people in the general population of the same age and sex[109]. The rate of abdominal aortic aneurysm in GCA patients is similar to that in the general population[109,110].

The rate of aortic aneurysm growth among individuals with GCA remains under investigation; a large cohort study found an average annual aneurysmal growth rate of 1.5 mm, increasing to 4.5 mm per year in those who later had dissections[111]. Additionally, 39% of patients who developed aortic dissection had a maximum aortic aneurysm width <50 mm (ref. 111). These findings suggest that surgical thresholds for aortic dilatation and aneurysm may differ in the GCA population compared with the general population, in which many dissections occur when the aorta is dilated to >50 mm. Baseline imaging of the aorta is typically performed in all patients newly diagnosed with GCA, according to the ACR–VF guidelines for the management of GCA[14]. Ongoing monitoring for aortic dilatation is recommended, although there is no consensus on the optimal imaging strategy or frequency. Transthoracic echocardiography is widely available, avoids exposure to radiation and can assess the ascending aorta size; however, the descending thoracic aorta is not evaluable by echocardiography. CT angiography and magnetic resonance angiography offer complete visualization of the aorta, although the cost–benefit ratio and optimal scanning interval remain unclear[112]. The ACR–VF guidelines recommend long-term clinical monitoring, whereas the EULAR guidelines recommend monitoring with imaging to detect structural damage. When initial imaging reveals abnormalities, the timing of subsequent studies depends on the type of pathology identified; for example, if an aortic dilatation or aneurysm is observed, follow-up imaging should consider the initial diameter and patient co-morbidities. Decisions regarding imaging frequency and modality are often made jointly with cardiovascular or thoracic surgery specialists.

Prevention of treatment-associated toxicity

Owing to the risk of serious and frequent glucocorticoid-related adverse effects, patients with GCA should have a management plan that addresses glucocorticoid toxicity. The risk of pneumocystis pneumonia (PCP) is increased in patients treated with high-dose glucocorticoids. Although this complication is rare in patients with GCA[113,114], some experts advocate PCP prophylaxis while patients are receiving moderate or high doses of glucocorticoids, given the potential for substantial PCP-related morbidity and mortality. Ultimately, the decision to initiate PCP prophylaxis should be an individualized one, taking into account patient-specific risk factors and preferences, and guided by a careful discussion of the potential benefits and risks. Trimethoprim–sulfamethoxazole is the first-line agent for PCP prophylaxis; alternatives include dapsone, atovaquone, or inhaled pentamidine if trimethoprim–sulfamethoxazole is contraindicated[114,115].

All patients with GCA receiving glucocorticoids should undergo baseline bone health evaluation, following guidelines for glucocorticoid-induced osteoporosis prevention and management[116].

Other recommendations, based on our own expert opinions, include periodic screening for hyperglycaemia and hypertension, along with dietary counselling for weight management. Patients with GCA should receive appropriate vaccinations, particularly pneumococcal and influenza vaccines. Herpes zoster vaccination is recommended, particularly for patients receiving a JAK inhibitor. Ophthalmological evaluation is recommended for those developing visual changes to differentiate between ocular GCA manifestations and GC-induced eye complications, particularly cataracts.

Polymyalgia rheumatica

General principles of polymyalgia rheumatica treatment

Many features of PMR predispose clinicians to diagnostic error: proximal pain and stiffness, systemic symptoms, distal musculoskeletal manifestations and elevated inflammatory markers are features shared with numerous other disorders that can mimic PMR. In the absence of a specific diagnostic test, diagnosis of PMR requires careful exclusion of alternative conditions at onset and throughout follow-up. Reliance on responsiveness to glucocorticoid therapy is also of limited use, as glucocorticoids can transiently alleviate symptoms of other diseases. Therefore, it is essential to distinguish true PMR from its many mimics before considering bDMARD therapy, which should be avoided in partial responders to glucocorticoid therapy until mimicking conditions and relevant comorbidities have been rigorously excluded.

The main goal of treatment in PMR is induction and maintenance of remission. Patient education and shared decision-making are essential. A suggested treatment algorithm for PMR is illustrated in Fig. 3.

Initial treatment with glucocorticoids. Glucocorticoids are the first-line therapy for PMR as they provide rapid relief from symptoms. However, relapses are common in PMR, and many patients require prolonged glucocorticoid therapy, with a substantial proportion remaining on treatment for 4–5 years after diagnosis. This high relapse rate

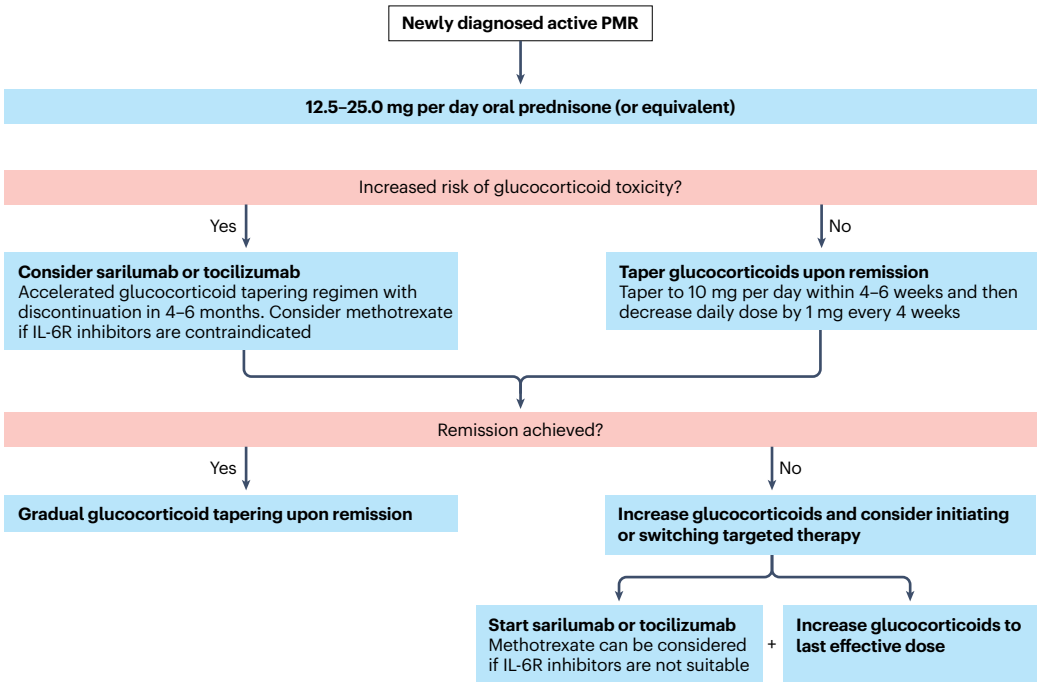

Fig. 3 | Treatment algorithm for polymyalgia rheumatica. This algorithm summarizes a pragmatic approach to the management of patients with polymyalgia rheumatica (PMR). Glucocorticoids remain the cornerstone of remission-induction therapy and are typically initiated at doses of 12.5–25 mg per day of prednisone (or equivalent), followed by gradual tapering once remission is achieved. IL-6 receptor (IL-6R) inhibitors such as sarilumab or tocilizumab can be considered in patients with relapsing or refractory disease or in those at an increased risk of glucocorticoid-related adverse effects. Methotrexate can be considered as an alternative glucocorticoid-sparing agent when IL-6R inhibitors are contraindicated or not suitable. Sarilumab is currently the only therapy specifically approved for the treatment of relapsing PMR. Treatment decisions should be guided by regular assessment of disease activity. In patients who do not achieve adequate disease control, escalation of glucocorticoid therapy and initiation or modification of targeted therapy can be considered, with treatment strategies individualized according to clinical response and comorbidities. Once remission is achieved, gradual tapering of glucocorticoids is recommended. In patients receiving glucocorticoid-sparing therapies, accelerated glucocorticoid tapering and earlier discontinuation could be feasible. In patients in a state of sustained remission receiving combination therapy, glucocorticoids are typically tapered first, whereas targeted or conventional immunomodulatory therapies are generally maintained longer before considering dose reduction or discontinuation.

and cumulative glucocorticoid exposure underscore the need for effective glucocorticoid-sparing strategies in PMR[117,118]. Recommended initial doses are 12.5–25 mg of prednisone equivalent once daily in the morning, which can be adjusted depending on patient comorbidities such as diabetes mellitus, heart disease or osteoporosis[119].

After remission, glucocorticoids are tapered gradually to 10 mg daily by 4–8 weeks and discontinued within 1 year if no relapse occurs. This approach typically results in cumulative doses of ~2 g of prednisone, exceeding the level associated with increased risk of infection and cardiovascular events[120]. However, some patients can sustain remission with shorter durations of glucocorticoid treatment.

The role of intramuscular and intra-articular glucocorticoids. Injections of glucocorticoids into the subdeltoid bursa or intramuscularly have been studied in PMR but are generally not used in clinical practice. A multicentre trial comparing intramuscular methylprednisolone acetate with oral prednisolone showed similar remission rates up to 96 weeks, but intramuscular methylprednisolone acetate resulted in lower cumulative glucocorticoid exposure, fewer fractures and less weight gain[121]. A separate study demonstrated that bilateral shoulder injections of methylprednisolone rapidly reduced pain, morning stiffness and inflammatory markers, with MRI-confirmed resolution of periarticular inflammation in responders and no significant adverse effects[122].

Traditional immunosuppressants as glucocorticoid-sparing agents. To prevent relapses and minimize glucocorticoid exposure and related adverse effects, several glucocorticoid-sparing agents have been used. According to the 2015 ACR–EULAR recommendations for the management of PMR, methotrexate can be considered for patients experiencing disease relapse, those with newly diagnosed PMR who are at a high risk of relapse, or those at risk of glucocorticoid-related adverse effects[119]. Evidence for methotrexate as a glucocorticoid-sparing agent has historically been inconsistent, with only two of four randomized trials meeting their primary end points for relapse prevention or glucocorticoid reduction[123–126]. These studies, however, used relatively low doses of methotrexate (7.5–10 mg per week), lower than the dose of 25 mg per week commonly applied in practice for the management of vasculitis and rheumatoid arthritis. More recently, a double-blind, placebo-controlled RCT[127] evaluated methotrexate at a dose of 25 mg per week in patients with newly diagnosed PMR who also received a standardized 24-week glucocorticoid taper. Methotrexate therapy significantly increased the proportion of patients who achieved glucocorticoid-free remission at 52 weeks compared with placebo,

supporting the potential benefit of introducing methotrexate early as a glucocorticoid-sparing strategy[127].

Other immunosuppressants, such as leflunomide and azathioprine, have shown some promise in small studies but sufficient evidence is lacking[24,128]. A phase III trial of leflunomide for PMR is ongoing (NCT03576794). These agents are not currently recommended as first-line treatments for PMR. NSAIDs and analgesics are not primary therapies but can help with coexisting degenerative pain.

Glucocorticoid-sparing agents

Pathophysiological rationale for the development of new treatment in polymyalgia rheumatica. A pathophysiological rationale for the development of new treatments in PMR is presented in Fig. 4. PMR almost exclusively occurs in individuals over 50 years of age, with peak incidence around 75 years of age, suggesting a strong link with ageing. Increased numbers of senescent lymphocytes (for example, $CD28^{-}NKG2D^{+}$ T cells) have been detected in the peripheral blood of patients with PMR[129,130]. Moreover, processes such as immunosenescence and inflammageing, endocrino-senescence (for example, reduced levels of dehydroepiandrosterone sulfate and cortisol) and age-related changes in gut microbiota could contribute to PMR pathogenesis[129,130]. Most patients with PMR exhibit systemic inflammation characterized by an increased acute-phase response and elevated serum concentrations of IL-6, B cell activating factor and CXCL9 and CXCL10 chemokines[131]. IL-6 is also one of the key mediators of immunosenescence and inflammageing; thus, drugs inhibiting the IL-6 signalling pathway have a rational basis for being used in PMR.

Despite alterations in peripheral B cell subset frequencies, and elevated plasma levels of immune complexes, no specific autoantibodies have been consistently linked to PMR, and B lymphocytes are rarely detected within inflamed tissues[132]. Consequently, the role of B cells and the possible presence of B cell niches in PMR remain unclear, although B cell-depleting therapies have been successfully tested in patients with PMR[133].

Other immune-cell subsets that have been reported to be dysregulated in the peripheral blood of patients with PMR include T_H1 cells, T_H17 cells and T_C17 cells (increased), regulatory T cells (decreased), natural killer cells (decreased), intermediate and classical monocytes (increased), and neutrophils (increased and with an activated phenotype); results regarding $CD8^{+}$ T cells are not clear[129,132,134–136].

Synovial fluid from patients with PMR usually shows mild to moderate leucocytosis, predominantly composed of mononuclear cells[137]. Increased frequencies of T_H1 ($CD4^{+}IFN\gamma^{+}IL\text{-}17^{-}$) cells and T_H1/T_H17 ($CD4^{+}IFN\gamma^{+}IL\text{-}17^{+}$) cells, but not T_H17 cells or T_C17 cells, have been observed in PMR synovial fluid, suggesting that there are differences in immune profiles between synovial fluid and peripheral blood compartments, and supporting the use of anti-IFNγ and possibly anti-IL-17 therapies[134]. Intermediate monocytes are particularly expanded in synovial fluid, and all monocyte subsets display an activated phenotype, with upregulation of CD64, CD80, CD86, CD206 and FRβ compared with paired peripheral blood monocytes[135]. Additionally, elevated levels of soluble mediators, including neuropeptides such as vasoactive intestinal peptide and pro-angiogenic molecules, have been reported in PMR synovial fluid[129].

Arthroscopy-guided synovial biopsy studies have revealed the presence of synovitis, characterized by leucocyte infiltration and vascular proliferation, in patients with PMR[138]. The infiltrating cells consist mainly of macrophages and $CD4^{+}$ T lymphocytes expressing HLA class II, whereas B cells, natural killer cells and γδ T cells are rarely detected. PMR synovial tissue is marked by expression of cytokines associated with myeloid cell activation and T_H1 cell differentiation (for example, IFNγ but not IL-17)[134], highlighting the T_H1 cell pathway as a potential therapeutic target in PMR. Macrophages and macrophage-associated cytokines, including IL-6, GM-CSF, M-CSF, IL-12, IL-23, IFNγ, TNF and IL-1β, are highly expressed in PMR synovial tissue, indicating that macrophages are major producers of pro-inflammatory cytokines in PMR tissues and key drivers of local inflammation[135]. On the basis of the findings of dysregulated cytokine expression, JAKs are probably activated and are emerging as potential therapeutic targets.

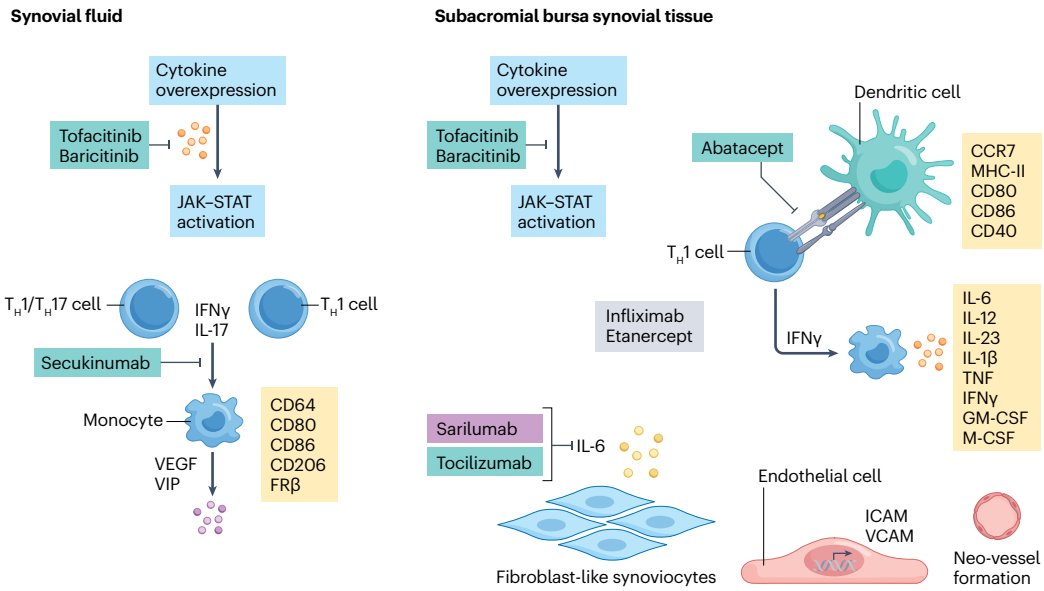

Fig. 4 | Pathophysiological rationale for the development of new treatments in polymyalgia rheumatica. The main contributors to the pathogenesis of polymyalgia rheumatica (PMR) in synovial fluid and synovial tissue are shown, along with respective therapies. Boxes filled in violet indicate the approved drugs. Boxes filled in green indicate the drugs under study. Grey boxes indicate the drugs that failed or that had limited activity. JAK, Janus kinase; T_H1, T helper 1.

Interleukin-6 blockade. The introduction of IL-6R inhibitors, particularly with the approval of sarilumab by the FDA and EMA in 2023 for the treatment of relapsing and refractory PMR, has led to preference being given to these agents over methotrexate in cases of PMR in which glucocorticoid-sparing is required[139,140]. This new approach to PMR treatment is supported by data from clinical trials as well as observations in clinical practice as outlined below[141–143].

Initial data on the potential efficacy of tocilizumab derive from two open-label studies involving a total of 30 patients with new-onset PMR[144,145]. In one of these studies, tocilizumab was used as monotherapy for the first 12 weeks, followed by oral prednisone therapy for weeks 12 to 24 (ref. 144). Although all 20 patients achieved a state of low disease activity by 12 weeks, this outcome occurred in only 9 (45%) after 4 weeks. As >70% of patients are expected to respond to oral glucocorticoid therapy within 4 weeks[146], it might be concluded that the effect of tocilizumab is delayed compared with glucocorticoids and that a combination of these drugs is required, at least for initial treatment of PMR.

Subsequent RCTs confirmed the promising results of the open-label studies. In the phase II–III PMR-SPARE trial[147], 36 patients with new-onset PMR were randomly allocated (1:1) to receive treatment with tocilizumab 162 mg per week or matching placebo; both groups received prednisone at a starting dose of 20 mg, which was tapered to 0 mg within 11 weeks. The primary outcome of glucocorticoid-free remission at week 16 was achieved by 63.2% of patients in the tocilizumab group but only 11.8% of the placebo group, and the median cumulative prednisone dose was almost 40% lower in the former group (781 mg versus 1,290 mg). The SEMAPHORE trial recruited 101 patients with glucocorticoid-dependent PMR (defined as PMR activity score (PMR-AS) >10 and the impossibility of reducing prednisone dose below 10 mg per day)[148], who received tocilizumab (8 mg/kg intravenously) or placebo every 4 weeks, with a rapid glucocorticoid taper. The primary end point was a composite of PMR-AS <10 and either an actual prednisone dose of ≤5 mg per day or a decrease in prednisone dose by ≥10 mg per day from baseline at 24 weeks. Compared with the placebo group, more patients in the tocilizumab achieved the primary end point (67.3% versus 31.4%) and were able to discontinue prednisone therapy (49% versus 19.6%). Treatment with tocilizumab did not, however, result in sustained treatment-free remission given that 92.3% of patients experienced a relapse a median of 15 weeks after discontinuation of tocilizumab[149].

Sarilumab was evaluated in the phase III SAPHYR trial of 118 patients with PMR and at least one relapse, although the target of 280 enrolees was not met because of the COVID-19 pandemic[150]. Participants were randomly allocated (1:1) to receive either sarilumab 200 mg subcutaneously every other week plus a 14-week glucocorticoid taper (starting dose 15 mg prednisone daily), or placebo plus a 52-week glucocorticoid taper. The primary outcome was sustained remission at 52 weeks, defined as resolution of PMR signs and symptoms by week 12, absence of a flare, CRP normalization and adherence to the glucocorticoid taper between weeks 12 and 52. More patients in the sarilumab group than in the placebo group achieved this end point (28.3% versus 10.3%); this finding was confirmed by a sensitivity analysis that excluded CRP from the primary outcome (remission rates 31.7% versus 13.8%). The cumulative glucocorticoid dose was lower in the sarilumab group than in the placebo group (777 mg versus 2,044 mg). Positive effects of sarilumab were also seen for health-related quality of life, function, fatigue and general health, as assessed by patients[151].

B cell targeted treatment. Even though the role of B cells in the pathogenesis of PMR is unclear, rituximab has been tested in the proof-of-concept BRIDGE-PMR trial of 47 patients (38 with new-onset and 9 with relapsing PMR), who received either a single infusion of 1,000 mg rituximab or placebo[133]. All patients were also treated with 50 mg intravenous prednisone followed by oral prednisone 15 mg per day and a subsequent rapid tapering regimen aimed at discontinuation of glucocorticoids at week 17. The primary end point was to achieve remission (PMR-AS <10) without glucocorticoids at week 21. Thereafter, patients were managed according to standard of care without further rituximab infusions and followed up until week 52 in an extension study[152]. Glucocorticoid-free remission was achieved more frequently by patients treated with rituximab (48% at week 21 and 52% at week 52) as compared with placebo (21% and 21%, respectively)[133,152]. Median cumulative prednisone dose at week 52 was lower in the rituximab group (1,595 mg versus 2,302 mg)[152]. Interestingly, the persistence of remission during follow-up without additional rituximab infusions could suggest a sustained therapeutic effect, raising the possibility of a disease-modifying effect, although this remains to be confirmed.

Janus kinase inhibitors. Tofacitinib and baricitinib are the only JAK inhibitors tested for treatment of PMR so far[153–155], although neither agent is currently approved by regulatory authorities for the treatment of PMR. Tofacitinib was first evaluated in a single-arm trial of 14 patients with highly active PMR (PMR-AS >17 and abnormal levels of acute-phase reactant). Tofacitinib was administered in conjunction with prednisone 15 mg per day, with the latter being tapered down to ≤2.5 mg per day within 20 weeks. The primary end point, PMR-AS <7 with prednisone dose ≤2.5 mg per day for 4 weeks from week 20 onwards, was achieved by 85.7% of the study participants[153]. Another study randomly allocated 39 patients to receive tofacitinib (without glucocorticoids) and 32 patients to receive glucocorticoids at a starting dose of 15 mg per day prednisone equivalent followed by a gradual taper according to current clinical practice[154]. All patients in both groups achieved the primary end point, which was low disease activity (PMR-AS <10) at weeks 12 and 24. The mean daily prednisone dose in the glucocorticoid arm, however, was 6 mg at 24 weeks.

Baricitinib was evaluated in the BATCHELOR trial, which involved 34 people with recent-onset (<6 months) PMR who had highly active disease (PMR-AS >17)[155]. Participants received either baricitinib at a dose of 4 mg or placebo for 12 weeks, followed by 2 mg baricitinib or placebo for a further 12 weeks. Notably, this study did not include oral glucocorticoids in the placebo arm, although two glucocorticoid injections at weeks 1 and 4 were permitted in both treatment arms and oral glucocorticoids were used as rescue treatment. The primary end point, PMR-AS ≤10 at week 12 without rescue therapy, was more frequently achieved by patients treated with baricitinib than by those who received placebo (77.8% versus 13.3%). Use of glucocorticoid rescue therapy was recorded in 66.7% of patients in the placebo group but only by a single patient (corresponding to 5.6%) in the baricitinib group. These findings highlight the strong clinical effect of JAK inhibition in PMR and suggest that future treatment strategies for PMR could be designed to minimize, or potentially avoid, the need for oral glucocorticoids. Response to baricitinib was rapid and persistent given that 52.9% of patients achieved PMR-AS ≤10 after 2 weeks and 76.5% remained in a state of low disease activity up to week 36 despite stopping baricitinib at week 24.

In both trials that tested JAK inhibitors without glucocorticoids[154,155], there was no safety alert in people receiving the study drug,

in particular, no cardiovascular or thromboembolic events; however, the follow-up time was too short and the sample sizes too small to draw any definitive conclusions.

Other biologic agents. Abatacept was evaluated in the ALORS trial involving 34 people with recent-onset PMR and high clinical disease activity[156]. The primary end point of low disease activity (defined as PMR-AS ≤10 at week 12 with no glucocorticoids and no rescue treatment) was achieved by 50% of patients treated with subcutaneous abatacept (125 mg weekly) and 22.2% of those who received placebo, but the between-group difference was not statistically significant ($P = 0.07$). Sub-analyses indicated, however, that the potential effect of abatacept on PMR-AS was related to a strong reduction of CRP level, which is an important component of this composite score. The cumulative glucocorticoid dose was similar in both groups.

Infliximab (3 mg per kg body weight) was investigated in a 52-week trial that included 53 patients with new-onset PMR[157]. The trial failed to demonstrate any benefit of adding infliximab to prednisolone concerning the primary end point (proportion of patients without relapse or recurrence through week 52) and key secondary end points including cumulative glucocorticoid dose[157].

Etanercept was compared with placebo in a trial of 20 patients with newly diagnosed PMR who were not being treated with glucocorticoids[158]. This trial failed to reach its primary end point, which was to demonstrate a greater reduction in PMR-AS at week 2 in the intervention group than in the placebo group.

In the REPLENISH RCT (the results of which are currently available only in an abstract), adults ≥50 years old with relapsing PMR were randomly allocated to receive treatment with secukinumab 300 mg or 150 mg or placebo for 52 weeks, all in combination with a 24-week prednisone taper. Both secukinumab regimens significantly increased the rate of sustained remission at week 52 compared with placebo (41.2% and 40.6% versus 20.4%) and reduced cumulative glucocorticoid exposure (adjusted annual dose 1,603.7 mg and 1,683.2 mg in the two secukinumab groups versus 2,093.0 mg in the placebo group).

The safety of secukinumab was consistent with its known profile, with no new safety signals. The preliminary results of the REPLENISH trial[159] suggest that secukinumab might be more effective in PMR than in GCA, although further data are needed to fully clarify its efficacy in GCA.

International recommendations for the treatment of polymyalgia rheumatica

Evidence-based guidelines for the management of GCA were released by the EULAR in conjunction with the ACR in 2015[119] and by several national scientific societies[139,140,160–162]. Although the EULAR recommendations are expected to be updated in the near future, updated guidelines from the rheumatology societies of France[139], Germany (together with the Austrian and Swiss societies)[140] and Norway[162] have been published within the past few years.

Current recommendations for the management of PMR support the initiation of oral glucocorticoids at a dose within a range of 12.5–25 mg prednisone equivalent daily, followed by gradual tapering once remission is achieved[119,160]. Whereas the 2015 ACR–EULAR recommendations advise use of the minimum effective individualized duration of glucocorticoid therapy in patients with PMR but do not include a maximum duration of therapy, the most recent German guidelines (published in 2025) recommend limiting glucocorticoid monotherapy to a maximum of 1 year, acknowledging the toxic effects of long-term glucocorticoid use[140].

The ACR–EULAR conditionally recommended considering the early introduction of methotrexate in patients experiencing a relapse of PMR and in patients with new-onset disease at a high risk of relapse, prolonged glucocorticoid exposure or glucocorticoid-related adverse events[119]. The more recent guidelines from France and Germany now include recommendations about when and how to use bDMARDs in PMR[139,140]. According to these guidelines, an IL-6R blocking agent should be used in patients with a relapsing disease course and can be used in selected patients with new-onset disease at a high risk of glucocorticoid-induced adverse effects; methotrexate (or rituximab) can still be used as an alternative. In patients treated with IL-6R blocking agents, discontinuation of oral glucocorticoids should be attempted after 16 weeks, and after 6–8 months in patients treated with methotrexate[140].

Routine monitoring of disease activity

There are currently no standard definitions of remission or relapse in PMR[11,136] (Box 1). Remission is generally defined as the absence of typical symptoms with normalized inflammatory markers. The PMR-AS is a validated composite measure of disease activity that can assist in standardizing assessments. Scores <10 are commonly considered indicative of low disease activity and can guide treatment de-escalation[163]. Relapse of PMR is defined by worsening of symptoms accompanied by elevated concentrations of acute-phase reactants. Isolated rises in ESR or CRP level are insufficient to diagnose relapse but warrant evaluation to determine the cause. There is no elevation in ESR in approximately 27% of relapses and no elevation in CRP level in approximately 14%[164]; relapses without elevation of these inflammatory markers are particularly relevant during treatment with IL-6R blockage.

Failure to respond to the standard starting dose of 12.5–25 mg prednisone equivalent should prompt evaluation for other conditions that mimic PMR, such as elderly-onset rheumatoid arthritis or malignancy, as well as concomitant infection or GCA[7,119,165].

T2T guidelines for PMR recommend that patients should be monitored every 1–4 weeks until remission is achieved, then every 3–6 months once they are in a state of stable remission; the frequency of follow-up after cessation of therapy is determined on an individual basis[7]. At every visit, patients should be assessed for pain, stiffness and mobility, and should undergo basic laboratory tests (ESR and/or CRP, blood count, glucose, and other assessments as needed) to monitor disease activity and drug toxicity.

Glucocorticoid-induced adrenal insufficiency can occur in long-term users, especially when prednisone is tapered below 7.5 mg/day, and can mimic relapse, leading to unnecessary treatment and increased risk of drug toxicity. Non-specific symptoms such as arthralgia, myalgia, malaise or fatigue with normal CRP level should raise suspicion of adrenal insufficiency, and when it is suspected, morning cortisol concentration should be checked; most cases of adrenal insufficiency resolve with slow glucocorticoid tapering[7,166].

Treatment of relapsing polymyalgia rheumatica

Relapses are generally early and common in PMR, affecting approximately half of patients within 1 year of treatment initiation; relapse often occurs when the prednisone dose drops below 10 mg per day, and each relapse prolongs glucocorticoid therapy[117,141]. Symptoms can resemble disease onset but are usually milder and can include isolated systemic or distal musculoskeletal manifestations[165,167,168]. In patients with an inadequate response to initial PMR treatment, persistent inflammation or frequent relapses, subclinical GCA should be considered, as it occurs in up to 23% of patients with PMR[169–172].

Glucocorticoid-sparing therapies should be considered in patients with relapsing PMR. Robust evidence suggests tocilizumab and sarilumab as valid alternatives to glucocorticoids[147,148,150], but optimal treatment duration and discontinuation strategies require further study. Currently, only sarilumab is approved by international regulatory agencies for refractory or relapsing PMR.

Prevention of treatment-associated toxicity for polymyalgia rheumatica

Long-term glucocorticoid therapy in PMR is associated with toxic effects including osteoporosis, hypertension, diabetes mellitus, infections and cataracts[136,165,173,174]. In a population-based cohort, 65% of patients treated with glucocorticoids alone experienced at least one adverse event, with cumulative doses ≥1,800 mg increasing the risk of adverse events[173]. Even low doses (≤5 mg per day) increase long-term cardiovascular risk[175]. Frailty due to chronic GC use is common[176]. Data from a 2025 prospective cohort study indicate that patients with PMR treated with glucocorticoids, particularly women, experience a decline in physical function over the first 2 years after diagnosis compared with age-matched and sex-matched individuals without PMR, highlighting the persistent impact of PMR on physical function despite appropriate glucocorticoid treatment and apparent disease control[177].

Prevention and management of glucocorticoid-related adverse events are therefore essential. Patients at a high risk of such events could benefit from the use of lower initial glucocorticoid doses and early introduction of glucocorticoid-sparing therapy. Recommendations for preventing and treating glucocorticoid-induced osteoporosis should also be followed[116]. Future studies should also focus on developing targeted muscle-conditioning programmes that could be integrated into routine care for patients with PMR.

Future perspectives for giant cell arteritis and polymyalgia rheumatica treatment

New agents in development

Drugs in development for the treatment of GCA and PMR are summarized in Table 1 and Table 2. As already mentioned, preliminary results of the phase III REPLENISH trial of secukinumab in PMR are reportedly positive[159]. Another drug in development is clofutriben, a selective inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD-1), which regulates the exposure of active intracellular glucocorticoids to their intracellular receptors; it is hoped that this drug will attenuate potential adverse effects of glucocorticoids. Early results of a phase II trial in PMR (published as an abstract) indicate that clofutriben mitigates the adverse effects of glucocorticoids on biomarkers of bone turnover, lipid metabolism, hypercoagulability, and cardiovascular and adrenal function, whilst maintaining their anti-inflammatory properties[178].

The failure of secukinumab to meet the primary end point in the phase III GCAptAIN trial in GCA is certainly disappointing and stimulates ongoing discussion about the design of drug trials in GCA and PMR[91]. The definition of clinical response, as well as the handling of

Table 1 | Ongoing randomized controlled trials in giant cell arteritis

Drug(s) evaluated	Trial description	Dose	Glucocorticoid tapering	Population	Primary end point	Trial number and status
Abatacept	Multicentre, randomized, double-blind, placebo-controlled phase III trial	Abatacept 125 mg weekly for 12 months	Protocol-specified 26-week glucocorticoid taper	78 patients with active, newly diagnosed or relapsing GCA	Remission at month 12	NCT04474847; recruiting
Tocilizumab versus methotrexate	Multicentre, randomized, open-label, controlled phase III trial	Tocilizumab subcutaneously 162 mg per week for 52 weeks, or methotrexate subcutaneously 0.3 mg/kg per week (without exceeding 20 mg per week) for 52 weeks	Protocol-specified glucocorticoid taper	230 patients with active, newly diagnosed or relapsing GCA	Relapse-free remission without deviation from the scheduled GCA regimen at week 78	NCT03892785; active, not recruiting
Methotrexate	Single-centre, randomized, double-blind, placebo-controlled phase II trial	Methotrexate subcutaneously 17.5 mg per week for 12 months	Glucocorticoids allowed only in the case of a relapse, tapered according to a protocol-specified regimen	52 patients with GCA in stable glucocorticoid-free remission, previously treated with tocilizumab for ≥6 months	Time to relapse during the 12-month treatment period	NCT05623592; active, not recruiting
Tocilizumab (gradual versus immediate discontinuation)	Multicentre, randomized, open-label, phase III trial	Tocilizumab subcutaneously 162 mg every 2 weeks from weeks 0 to 12 then 162 mg every 4 weeks until week 24, or immediate cessation of tocilizumab	Glucocorticoids allowed only in the case of a relapse	120 patients with GCA in glucocorticoid-free remission; tocilizumab initiated 12–36 months prior to randomization	Relapse-free survival at week 26	NCT06037460; active, not recruiting
Tocilizumab (dose reduction versus discontinuation)	Multicentre, randomized, open-label, phase II trial	Tocilizumab intravenously 4 mg/kg monthly or subcutaneously 162 mg every 2 weeks for 18 months	Glucocorticoids allowed only in the case of a relapse	78 patients with GCA in glucocorticoid-free remission on tocilizumab; tocilizumab initiated ≥12 months prior to randomization	Sustained remission at month 18	NCT07108387; recruiting

GCA, giant cell arteritis.

Table 2 | Ongoing randomized controlled trials in polymyalgia rheumatica

Drug	Study description	Dose	Glucocorticoid starting and tapering dose	Population	Primary end point	Trial number and status
Leflunomide	Multicentre, randomized, double-blind, phase III trial	20 mg per day	Prednisolone 15 mg per day, tapered gradually to 0 mg per day by week 27	94 patients with newly diagnosed PMR	Number of relapses within 12 months	NCT03576794; unknown
Low-dose IL-2	Single-centre, open label, phase II trial	One million units of rhIL-2 subcutaneously 5 days per week for 4 weeks, then once per week for 8 weeks	Prednisone ≤10 mg per day or equivalent at study entry; prednisone-tapering regimen undefined	15 patients with PMR	Percentage change in FOXP3$^+$ T_{reg} cells at week 12	NCT04062006; unknown
Rituximab	Single-centre, randomized, parallel assignment, phase III trial	Rituximab single intravenous infusion of 1,000 mg	Unable to taper prednisolone below 5 mg/day (or equivalent); tapering regimen undefined	174 patients with relapsing PMR	Proportion of participants in glucocorticoid-free remission (PMR-AS <10) at week 52	NCT05533164 (REDUCE-PMR-2); active, not recruiting
Baricitinib	Multicentre, randomized, double-blind, parallel group, phase III trial	Baricitinib oral tablet 4 mg per day	Prednisone 20 mg per day, followed by a rapid pre-specified tapering regimen (details not defined)	46 patients with newly diagnosed PMR	Proportion of participants who achieve glucocorticoid-free remission at week 16	EudraCT 2020-005081-34 (JAK SPARE1); active
Tofacitinib	Single-centre, open-label, randomized, phase III trial	Tofacitinib oral tablet at a starting dose of 10 mg per day	Prednisone 15 mg per day, discontinued within 4 weeks	98 patients with PMR	Proportion of participants with PMR-AS score <10 at week 52	NCT06172361 (ITTGPMR); recruiting

PMR, polymyalgia rheumatica; PMR-AS, polymyalgia rheumatica activity score; rhIL2, recombinant human IL-2; T_{reg} cells, regulatory T cells.

(and alternatives to) acute-phase reactants in studies testing drugs that directly influence these parameters, are matters of ongoing debate[12]. The ACR and EULAR are currently supporting a project to develop new response criteria for GCA, and other international organizations such as OMERACT are developing instruments to measure disease activity as well as criteria to define remission and relapse in GCA and PMR[11,179,180].

Potential implications of the giant cell arteritis–polymyalgia rheumatica disease spectrum concept

Although drug trials to date have mostly been designed separately for GCA and PMR, the possibility of including patients with both diseases in the same trial has been discussed, given the pathophysiological and clinical overlaps between the two conditions and to enable faster recruitment to a given study[2]. However, PMR is clinically heterogeneous and although a subset of patients has subclinical vasculitis, the majority of patients with PMR have a musculoskeletal condition that would warrant a treatment approach different from that for GCA. Indeed, it is well known that there are still fundamental differences in treatments (such as glucocorticoid starting doses and tapering regimens as well as use of glucocorticoid-sparing agents) and outcome assessments between GCA and PMR[15,119].

The role of imaging in the optimal treatment of giant cell arteritis and polymyalgia rheumatica

Although the role of imaging in GCA for diagnostic purposes has been well established, there is ongoing uncertainty regarding treatment stratification based on disease involvement revealed by imaging. For instance, whether a patient with cranial GCA and no large-vessel involvement should receive the same induction and maintenance treatment regimen as a patient with both cranial and large-vessel involvement or a patient with only large-vessel disease is an unresolved question. Moreover, questions remain regarding the role of imaging in the diagnosis of PMR. Although imaging is not routinely required for the diagnosis of PMR, PET–CT is useful in selected situations, such as diagnostic uncertainty, atypical presentations or suspected large-vessel involvement[181].

The utility of imaging for monitoring disease activity, assessing vascular damage and predicting prognosis in GCA and PMR also remains to be fully defined[107,182]. The OMERACT GCA ultrasound score, for example, has demonstrated sensitivity to change in observational studies and to predict future relapses and glucocorticoid requirements[179,183]. However, the optimal frequency of ultrasonography assessments, particularly once patients have reached clinical remission, is still unclear. Similarly, there is no consensus about the frequency and the methodology for the assessment of vascular damage, particularly regarding aortic dilation. Although progress has been made in understanding which patients are at an increased risk of aortic aneurysm formation (for example, those with aortitis as revealed by PET imaging at baseline)[108], longitudinal imaging studies stratifying patients according to aneurysm risk are needed. A further area of uncertainty is the screening of patients with PMR for subclinical vasculitis. Although some studies indicated that patients with vascular inflammation verified by ultrasonography have higher relapse rates and greater glucocorticoid requirements, a study screening patients with PMR using PET–CT did not confirm these results[170,184].

Treatment duration and glucocorticoid tapering and discontinuation

On the research agenda is also the determination of the optimal duration of glucocorticoid treatment in GCA and PMR as well as the characterization of patients in whom glucocorticoid-sparing agents should be commenced. Although T2T recommendations suggest using the minimum effective dose and duration of drugs[7], and recent trials indicate that IL-6R blocking agents (in GCA and PMR) and upadacitinib (in GCA) considerable reduce glucocorticoid exposure[62,84,150], it is still not clear whether glucocorticoid-sparing agents should be prescribed to all patients with these diseases. In addition, the optimal duration of treatment with conventional immunosuppressants, bDMARDs and tsDMARDs, as well as strategies for their tapering and discontinuation, remain poorly defined. In particular, it is unclear whether such approaches would be cost-effective and how many patients could be

spared from glucocorticoid-related long-term damage. Furthermore, whether current therapies are truly 'disease-modifying' remains largely unknown. Patients ultimately deserve therapies that can shorten the disease course, prevent vascular complications in GCA and minimize the burden of immunosuppression.

Conclusions

The therapeutic landscape of GCA and PMR has evolved substantially over the past decade. Although glucocorticoids remain the cornerstone of treatment, advances in the understanding of disease pathogenesis have led to the development of targeted therapies that can reduce glucocorticoid exposure and improve disease control in selected patients. Nevertheless, key questions remain regarding patient selection for targeted therapies, optimal treatment duration, prevention of vascular damage progression, strategies for tapering glucocorticoids and immunomodulatory agents, and the role of imaging in guiding treatment decisions and monitoring long-term outcomes.

Beyond clinical efficacy, the future management of GCA and PMR will depend on improving the accessibility and appropriate use of targeted therapies. Despite growing evidence supporting the use of bDMARDs and tsDMARDs, their availability in routine practice varies across health care systems owing to differences in regulatory approval, reimbursement policies and cost. Further studies assessing their long-term effectiveness, safety and cost-effectiveness in real-world settings will be essential. In parallel, strategies to identify patients most likely to benefit from early targeted therapy, together with optimized T2T approaches, could help to balance clinical benefit, treatment burden and health care resource utilization.

Published online: 20 May 2026

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Acknowledgements
This article is dedicated to Gene G. Hunder, rheumatologist and clinical scientist, who has been one of the pioneers in the field of polymyalgia rheumatica and giant cell arteritis.

Author contributions
C.S., F.M., K.J.W., C.D., B.H. and S.C. researched data for the article and wrote the article. All authors made a substantial contribution to discussion of the content and to the review/editing of the manuscript before submission.

Competing interests
F.M. has received consulting fees and/or speaker honoraria from AbbVie, Amgen, AstraZeneca, CSL Vifor and GSK, and has received royalties from UpToDate. K.J.W. has received clinical trial support from BMS and consulting fees from Amgen, AstraZeneca and Sanofi. C.D. has received consulting fees and/or speaker honoraria from AbbVie, Fresenius, Janssen, Novartis, Sanofi and Sparrow. M.C.C. has received consulting fees from AbbVie, Alexion, AstraZeneca, Boehringer-Ingelheim, CSL-Vifor, GSK, Novartis and Royalty Pharma, and royalties from UpToDate. B.H. has received honoraria for advisory services from AbbVie, Alexion, AstraZeneca, Boehringer, BMS, Chugai, CSL Vifor, GSK, Novartis, Sanofi and Visterra, and honoraria for lectures from AbbVie, AstraZeneca, Boehringer, GSK, Pfizer, Medac, Novartis and Vifor Fresenius Medical Care Renal Pharma. A.W.M. has received consultancy fees payable to her institution from AstraZeneca, CSL Vifor, Glaxo Smith Kline, Roche/Chugai and Sanofi/Regeneron, outside the submitted work, and research and educational funding from Kiniksa Pharmaceuticals and Roche/Chugai, outside the submitted work. S.C. declares no competing interests. C.S. has received consulting fees and/or speaker honoraria from AbbVie, Amgen, AstraZeneca, Boehringer, CSL Vifor, GSK and Novartis, and royalties from UpToDate.

Additional information

Peer review information *Nature Reviews Rheumatology* thanks Claire Owen, who co-reviewed with Victor Yang; Maria Sandovici; and Marina Scolnik for their contribution to the peer review of this work.

nature reviews rheumatology

https://doi.org/10.1038/s41584-026-01380-8

Review article

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Decoding variants of uncertain significance in systemic autoinflammatory diseases

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Abstract

The development and implementation of genetic testing has revolutionized the diagnostic landscape of autoinflammatory diseases, leading to an exponential increase in the identification of disease-associated genetic variants. Yet a substantial proportion of these are considered variants of uncertain significance (VUS), complicating both diagnosis and therapeutic decision-making. This challenge is relevant not only for monogenic systemic autoinflammatory diseases, but also in the context of genetically complex disorders that can involve multiple low-penetrance variants. Advances in protein structure prediction tools, machine learning and artificial intelligence provide powerful computational frameworks for the classification of variants; however, their predictive accuracy must be benchmarked against functional assays, particularly with respect to gain-of-function variants. Functional screening approaches benefit from both technological progress and expanding knowledge of the innate immune pathways underlying systemic autoinflammatory diseases. Large-scale analyses of variants including multiplexed functional assays and deep mutational scanning experiments have enabled the assessment of hundreds of variants, notably in *NLRP3*, *MEFV* and *ADA2*, generating datasets that improve variant interpretation and genetic diagnosis. Altogether, these advances increase the potential of accurately predicting in the near future the effects of missense VUS, although numerous challenges remain to be addressed, especially those concerning our understanding of the influence of non-coding VUS in systemic autoinflammatory diseases.

Sections

Introduction

Decoding variants of uncertain significance through human genetics

Decoding variants of uncertain significance via in silico predictions

Decoding variants of uncertain significance via functional tests

Decoding variants of uncertain significance through the clinical phenotype

Translational implications

Conclusions

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Key points

- Variants of uncertain significance (VUS) remain a major issue in genetic investigations of systemic autoinflammatory diseases (SAIDs) and are responsible for a substantial proportion of diagnoses being inconclusive.
- The expansion of public exome databases has improved the functional classification of variants based on allele frequency; however, positive selection can increase the population frequency of pathogenic alleles in SAID genes, potentially complicating variant interpretation.
- Computational approaches to identifying pathogenic SAID-associated variants have vastly improved in accuracy owing to the development of 3D protein structure prediction and deep-learning methods, although they largely fail to predict gain-of-function variants.
- The large diversity of mechanisms underlying pathogenic variants in SAIDs has necessitated the development of tailored multi-scale functional assays.
- The eradication of VUS will require a multidisciplinary and integrative approach involving the generation of high-quality datasets of SAID-associated variants to benchmark and train deep-learning methods.
- Additional challenges include unravelling the contribution of VUS to complex SAIDs and understanding the effects of VUS in non-coding regions.

Introduction

Systemic autoinflammatory diseases (SAIDs) are characterised by systemic inflammation, recurrent fever and, depending on the condition, organ-specific symptoms such as serositis or cutaneous rash[1–3]. SAIDs can arise from inborn errors of immunity (IEIs; caused by germline variants in single genes)[4], somatic variants or complex (polygenic or multifactorial) mechanisms. These diseases remain challenging to diagnose, and genetic sequencing is required to support diagnosis of monogenic SAIDs. A wide range of sequencing approaches is currently used, each having specific strengths and limitations that influence both detection and interpretation of variants. Targeted gene panels focus on a predefined and limited set of genes (typically fewer than 300; see ref. 5 for an example of a panel of SAID-associated genes). Gene panels achieve high sequencing depth, allowing for sensitive detection of variants present in only a small proportion of a patient's cells through mosaicism (that is, low-level mosaic variants)[6]. However, their restricted scope inevitably means that variants located outside the selected genes are missed. Broader genomic approaches include whole-exome sequencing (WES) and whole-genome sequencing (WGS). WES targets the coding regions of all known genes, whereas WGS provides the most comprehensive coverage, including both coding and non-coding regions, and enables the detection of a wide spectrum of variant types, including intronic and regulatory variants that could be missed by panel-based or exome-based approaches. The broad scope of WES and WGS is associated with the detection of an increased number of variants, notably including variants of uncertain significance (VUS)[7,8], whereas their lower sequencing depth limits the detection of low-level mosaic variants. The reported diagnostic yields from clinical WES and WGS vary by indication, reaching approximately 30–40% in IEIs and around 20% in SAIDs, representing an increase in the yield of genetic diagnoses of ~5% compared with targeted gene panel methods[8–10]. Although a subset of WES and WGS is diagnostically decisive, a large proportion of variants, including VUS, require further evaluation.

Taken together, the widespread adoption of clinical sequencing has transformed clinical practice, but has also led to the identification of thousands of VUS in known SAID-associated genes (Supplementary Table 1) as well as in new candidate genes[4]. Genetic variants are classified as VUS when the available evidence is insufficient to classify the variant as either (likely to be) pathogenic or benign, based on established criteria such as population data, computational predictions, functional studies and segregation analysis (see Box 1). The resulting diagnostic uncertainty often leaves patients without a definitive molecular explanation for their symptoms and hampers rational therapeutic decision-making. Functional characterization of VUS therefore remains an important unmet need and a major challenge for geneticists, computational scientists and immunologists working on SAIDs.

In the past decade, knowledge of genetic variation in the general human population has expanded considerably, encompassing unprecedented global diversity, as exemplified by resources such as the Genome Aggregation Database (gnomAD)[11]. In parallel, an increase in the accuracy of 3D protein structure prediction[12,13] and the rise of artificial intelligence (AI) have enabled the development of novel in silico prediction tools[14,15]. Furthermore, progresses in synthetic biology and the advent of large-scale functional screens such as multiplexed assay of variant effect (MAVE) experiments[16] coupled with high-throughput sequencing offer new capacities to functionally classify variants on the basis of in vitro assays[16]. Synergistically, these advances provide new opportunities to functionally characterize, or 'decode', VUS with unmatched accuracy.

This Review focuses on novel approaches to decoding missense VUS, covering lessons from genetics, in silico prediction tools, functional assays and clinical observations, and highlighting their limitations. Specific examples of genes associated with SAIDs (excluding interferonopathies) are used to illustrate the successes and the technological obstacles in decoding VUS, classifying them and disseminating knowledge. Last, we outline a roadmap for clinicians, computational scientists and immunologists to improve future interpretation of VUS in the context of SAIDs.

Decoding variants of uncertain significance through human genetics

In a cohort of more than 1.5 million people who had been referred for genetic investigations, 41% of the participants tested had one or more VUS, and more than 30% of the initial genetic tests identified solely VUS[17]. The number of VUS per individual increases with the number of genes tested, and the majority of VUS (86.6%) are missense variants[17]. The prevalence of VUS and their influence on inconclusive diagnoses has been documented in multiple independent studies[18,19]. This issue is similarly highlighted by interrogation of public databases of variants such as Infevers, a registry of variants, with a focus on genes involved in SAIDs, that classifies variants on the basis of both international guidelines (Box 1) and expert consensus[20], and the ClinVar database, which reports human genetic variants across all known genes, classified for diseases and drug responses, with supporting evidence and no centralized curation[21]. Depending on the gene considered, the proportion

Box 1 | International guidelines for the interpretation of variants

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology have developed guidelines to standardize the classification of genetic variants[7]. Variants are assigned to one of five categories: benign, likely to be benign, uncertain significance, likely to be pathogenic and pathogenic[12,128]. These categories are assigned in the context of a specific disease and inheritance pattern. Six types of evidence are considered: population data (allele frequency); computational (in silico prediction) data; functional data; segregation analysis data; de novo variant data and allelic data (that is, whether the variant is observed in *cis* or *trans* with a pathogenic variant).

The qualitative American College of Medical Genetics and Genomics–Association for Molecular Pathology guidelines were transformed into a quantitative scoring system using a Bayesian framework[179]. Each line of evidence is weighted numerically for pathogenicity (with a weight of 8 indicating 'very strong' and 1 'supporting' evidence) or benignity (with a weight of −4 indicating 'strong' evidence) and incorporated into a Bayesian framework to generate a classification, with positive scores being associated with pathogenicity (for example, 6–9 indicates likely to be pathogenic) and negative scores with benignity[128–130]. As an example, segregation evidence is scored between −0.45 and +0.45 (ref. 180). Segregation of the variant with the disease in 3–4 or in ≧7 affected individuals will yield a score of +0.15 or +0.45, respectively. Conversely, apparent non-segregation in another affected individual in the case family (that is, the absence of the variant in this individual) will yield a negative score of −0.45 (ref. 180). Similarly, the score associated with functional assays is dependent on the robustness of the test and, notably, on the number of controls (a mix of benign and pathogenic variants) included as a validation of the assay[181].

Apart from variants found in the general population with an allele frequency >5% (automatically classified as benign), a minimum of two criteria is required for classification, underscoring the importance of combining multiple types of evidence, including both scientific and clinical data. Importantly, variant classification should be undertaken independently from previously published classifications (for example, those on Infevers or ClinVar), which are often out of date.

of VUS ranges from 4% to 62.5% in Infevers and from 23.3% to 89.7% in ClinVar (Supplementary Table 1). These numbers do not substantially change when only the recurrent fever genes identified more than 20 years ago (*MEFV*, *MVK*, *NLRP3*, *NOD2*, *PSTPIP1* and *TNFRSF1A*) are considered.

Lessons from human genetic variations

Population databases developed by the Broad Institute, beginning with ExAC in 2017 (encompassing 60,000 exomes)[22], followed by gnomAD v2 in 2020 (ref. 23), gnomAD v3 in 2024 (76,156 genomes)[24] and the current gnomAD v4 (spanning 807,000 exomes and genomes from individuals of diverse genetic ancestry), have become important tools in genetic diagnostics and have greatly changed the approach to the reporting and interpretation of variants over time. Metrics such as Z-score for missense variants indicate constraint (that is, intolerance to variation). Transcripts with high missense Z-scores carry fewer variants than expected based on the average mutation rate in population databases, suggesting that these transcripts are intolerant to missense mutations and that missense variants in the corresponding genes have a high probability of being pathogenic[25]. The negative selection of human pathogenic variants is particularly important in autosomal-dominant diseases, although genes underlying recessive disease and those that cause lethality before reproductive maturity also demonstrate negative selection pressures[26]. GnomAD now supports the classification of variants with an allele frequency >5% in the database population as 'benign'[7]. The rarity or absence of a given variant in these databases constitutes one of the criteria supporting the classification of a variant as 'pathogenic'. However, it is important to recognize that each individual has tens of 'private' (that is, unique) coding variants (for instance, an analysis of >195,000 individuals across the gnomAD v2 and v3 datasets found a mean of 27 ± 13 unique coding variants per individual[11]) and that common variants in an immunity-related gene can still have a pathogenic effect. Immunity-related genes (which are highly represented in monogenic SAIDs) are one of the classes of genes with the strongest evidence of positive selection (and genetic innovation), attributed to the 'arms race' between pathogens and the immune system[27], and this specificity should be kept in mind when assessing VUS using allele frequency (see Box 2).

Aside from *MEFV* variants, other 'frequent VUS' have been reported in genes associated with hereditary recurrent fevers, for which population data and functional evidence are discordant. For example, detection of the p.V198M or p.Q703K variants in the *NLRP3* gene does not enable a definitive diagnosis of cryopyrin-associated periodic syndrome (CAPS)[28]. Functional assays performed on these variants show that, although they promote a mildly hypermorphic phenotype, they are not as strongly activating as known pathogenic variants[29,30]. These 'frequent VUS' are therefore currently regarded as low-penetrance variants or inflammatory susceptibility factors rather than pathogenic variants[31]. Interestingly, these variants might contribute to complex SAIDs, illustrating how the study of VUS in monogenic diseases can provide information about the potential genetic contribution to complex SAIDs (see Box 3). Assessing penetrance involves the integration of genetic, clinical and sometimes environmental data to determine whether a variant consistently causes disease in carriers. Incomplete penetrance can complicate the interpretation of variants, particularly for rare or late-onset conditions. Furthermore, careful interpretation of population data is required, as the latest version of gnomAD, v4.1.0, disproportionately includes patients from clinical cohorts, including at least five individuals with STING-associated vasculopathy with onset in infancy, a severe interferonopathy. In addition, the frequency of a given variant needs to be assessed in the context of the ethnic group (or genetic ancestry) of the patient[28]. Despite recent efforts, minority ethnic groups are still under-represented in most public biobanks[32,33], which lowers the accuracy of genetic diagnosis in patients from these populations.

Although patients and diseases are usually the starting point to look for a genetic cause, the study of rare variants in relation to plasma protein levels in the UK biobank, a database containing genetic, health and lifestyle data from approximately half a million participants, identified rare variants in *NLRC4* (ref. 34). Gain-of-function (GoF) variants in

Box 2 | Positive selection of variants during evolution: the example of *MEFV*

Pathogenic variants are usually very rare in the human population. Yet several pathogenic *MEFV* variants (such as p.M694V and p.V726A) that cause familial Mediterranean fever (FMF) are present at a high frequency in certain Mediterranean populations. These variants have been positively selected in the human population during plague pandemics that killed up to 50% of the population[182]. Indeed, they conferred an evolutionary advantage to the individuals bearing them, by enabling their immune system and notably the pyrin inflammasome (pyrin being encoded by *MEFV*) to have a faster and stronger response to *Yersinia pestis* than the immune system of individuals with 'wild type' *MEFV* variants[40,183]. Besides these clearly pathogenic variants, the *MEFV* p.E148Q variant is also common in the human population (28% in individuals of South Asian ancestry) although with no evidence of positive selection[183]. This variant is generally considered a functional polymorphism rather than a cause of clinical FMF[184]; however, it enhances pyrin inflammasome activation when present on the same allele as p.M694I (that is, as a complex allele)[185] and thus cannot be classified as benign, despite its high frequency. Similarly, in numerous non-human primates, pyrin proteins bear amino acid sequences that are present in humans only in patients with FMF[186]. As a striking example, the pyrin protein from Tarsiers (small primates living in Southeast Asia) presents two well characterized FMF-causing mutations (p.M680I and p.V726A)[186]. Altogether, these observations suggest that pyrin has been under strong positive selections in the human population but also in related species, probably with species-specific pathogens, thus impairing the use of methods based on conservation or allele frequency to accurately predict the functional impact of these variants.

NLRC4 cause autoinflammation with infantile enterocolitis (also known as NLCR4 macrophage activation syndrome) or familial cold autoinflammatory syndrome (FCAS), typically characterized by increased levels of IL-18 (refs. 35–38). The study showed that increased IL-18 levels were associated with the p.Asp1009Tyr variant (identified in 0.01% of individuals in the UK biobank) and that decreased IL-18 levels were associated with two presumably loss-of-function (LoF) or hypomorphic variants (p.Trp30GlyfsTer4 and p.Gly786Val, present in 0.05% and 0.5% of UK biobank individuals, respectively)[34]. Whether these *NLRC4* VUS and the magnitude of IL-18 level changes observed could contribute to autoinflammation or susceptibility to infections remains to be demonstrated.

Lessons from genetic inheritance

When a novel VUS is identified, the first data considered are family history and segregation analysis. The observation that a variant has arisen de novo or segregates with the disease in several family members or across multiple families is considered supportive evidence for pathogenicity. However, incomplete penetrance is common in SAIDs and presents an additional challenge to the accurate classification of variants, as does the exhibition of multiple modes of inheritance within a single gene. In the case of *MEFV*, the presence of two pathogenic alleles, each inherited from one parent, establishes the genetic diagnosis of FMF. Nevertheless, some patients carry only one pathogenic *MEFV* variant and still fulfil the Eurofever–PRINTO clinical criteria for the disease and usually respond to colchicine therapy[39]. FMF-associated variants are hypermorphic, and specifically lower the activation threshold of the pyrin inflammasome[40]. Monocytes from patients carrying biallelic pathogenic *MEFV* variants display a stronger pyrin inflammasome response than monocytes from patients with a single pathogenic variant, indicating a gene-dosage effect that could explain why some heterozygous carriers are symptomatic with a less severe clinical phenotype[39–41]. Some cases of dominant inheritance linked to specific single *MEFV* variants have also been described[42]. These newly described dominant pyrin-associated autoinflammatory diseases have opened the way to the identification of low-level mosaic variants, which could arise during embryonic development or later in life[43]. Somatic variants have been found in several SAID-associated genes including *MEFV*[43], *UBA1* (ref. 44) (see Box 4), TNFRSF1A[45], *NLRC4* (refs. 46,47), and *NLRP3* (refs. 48,49). Comparative analyses of NLRP3 inflammasome activity of pathogenic variants that are germline, mosaic or both revealed that variants detected exclusively in mosaic form led to higher functional NLRP3 activity than those present in the germline[29,30,48]. This increased activity could account for the ability of mosaic variants to produce clinical phenotypes comparable with those produced by germline variants, despite very low variant allele frequency (often <10%) in leukocytes from affected patients[29,30]. Conversely, some somatic variants could be incompatible with life if present as germline variants owing to their phenotypic effects, potentially explaining why the repertoire of pathogenic variants in the mosaic and germline states does not fully overlap[48]. Although genetic investigation was historically restricted to children, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome and inflammatory syndromes associated with clonal haematopoiesis of indeterminate potential (CHIP) are newly discovered adult-onset diseases for which decoding VUS could be important (see Box 4).

Given the complex genetic status of each variant, understanding inheritance patterns and performing in-depth characterization through in silico predictions and functional assays are essential for the proper classification of novel variants.

Decoding variants of uncertain significance via in silico predictions

Despite a wealth of genetic information, our ability to reliably distinguish pathogenic from benign variants remains limited. Computational approaches (Table 1) have become essential to helping to bridge this gap on a large scale. Most models seek to predict the functional consequences of missense variants (single amino acid substitutions) at the protein level, whereas more complex genetic variants (for example, the deletion or insertion of multiple amino acids or non-coding variants) remain poorly addressed by computational techniques and are not covered in this Review.

Established computational predictors

Computational approaches developed in the 2000s[50] (for example, SIFT[51]) focused on single biological signals (Fig. 1) across several different categories: evolutionary conservation, under the assumption that residues that are highly conserved (for example, from flies to humans) are functionally essential; structural stability, which evaluates how mutations disrupt folding or molecular interfaces; and population allele frequency, as variants common in healthy individuals are considered likely to be benign. Each of these signals provides valuable but incomplete information. Some variable residues are functionally

critical and disease causing, despite a low degree of conservation across species. Many clinically relevant proteins (including important SAID-associated proteins) lack experimentally resolved structures and contain intrinsically disordered regions (IDRs; see Supplementary Fig. 1 and further discussion below), limiting the utility of structure-based models. Population frequency and evolutionary conservation data can be misleading, as they can be shaped by positive selection rather than benignity (see Box 2).

Consensus ensemble methods (for example, REVEL[52]) — often referred to as metapredictors — were then developed in the 2010s to combine predictions from multiple individual tools (and biological signals), improve robustness and maximize the strength of evidence of pathogenicity. These metapredictors, widely used in clinical laboratories[53], are analogous to seeking several medical opinions before reaching a diagnosis.

Novel deep learning and integrative models

The latest generation of tools for variant classification (for example, AlphaMissense[15]) is grounded in AI and deep learning (DL), which provide the extraction of complex correlations within proteins that were previously inaccessible to traditional approaches. A notable exception is PRESCOTT[14], which does not rely on deep neural-network architectures but instead directly reconstructs mutational landscapes by integrating protein sequence, structural models and allele-frequency data from human populations, thereby bringing together evolutionary, structural and population-level information in a unified framework. Modern predictors leverage diverse inputs such as sequence features, multiple sequence alignments capturing evolutionary conservation and coevolution, structural properties, allele frequency data and occasionally entire-genome context. By unifying these heterogeneous inputs — and, in some instances, explicitly modelling epistatic interactions among mutations — these tools are aimed at more faithfully representing the biological complexity underlying variant functionality[14].

These computational methods can be broadly categorized into supervised, unsupervised or semi-supervised machine-learning approaches (Table 1). Supervised computational models are trained on datasets of variants already classified as benign or pathogenic. These models learn distinguishing patterns that can then be applied to predict the likely classification of novel variants[50,54]. By contrast, unsupervised models do not rely on labelled data but instead identify statistical patterns within large datasets, flagging variants that deviate from these patterns as potentially deleterious. Semi-supervised models integrate elements of both strategies by training on a small set of curated pathogenic and benign variants while simultaneously exploiting patterns present in much larger unlabelled variant datasets to improve predictions. Many computational tools now provide pre-computed pathogenicity scores for all possible human missense variants, enabling direct interpretation of newly identified variants. In addition, novel tools such as Variant-to-Phenotype (V2P) incorporate clinical phenotypes as output and during model training to improve prediction of both variant prediction and disease[55].

Over time, evolutionary signals have proven to be amongst the most powerful indicators of pathogenicity. Conservation patterns across species highlight residues subject to strong structural or functional constraint, and coevolutionary relationships between positions within a protein capture compensatory mutations that preserve stability or activity[56]. Models capable of exploiting these dependencies have shown improved predictive accuracy compared with models focusing only on human protein variants[57]. DL methods are well suited to detecting and modelling such complex relationships, with neural networks being particularly effective at identifying coevolutionary signals. Advances in DL have further enabled integrative

Box 3 | Complex systemic autoinflammatory disease: variants of uncertain significance in Still's disease pathogenesis

Despite considerable advances in understanding systemic autoinflammatory diseases (SAIDs), the pathogenesis of Still's disease remains incompletely defined. The hallmark features of this rare condition are spiking fever, rash and arthritis, but nearly any organ system can be involved, leading to frequent diagnostic uncertainty. Its clinical overlap with monogenic SAIDs and its strong therapeutic response to cytokine blockade, particularly IL-1 and IL-6 inhibition[187,188], provide important clues that innate immune dysregulation is central to Still's disease.

Genetic analyses reinforce these observations. In a large cohort[189], more than half of the patients with Still's disease were found to harbour multiple rare germline variants in genes associated with monogenic SAIDs and also clonal haematopoiesis of indeterminate potential (see Box 4). These variants were not restricted to classical hereditary periodic fever genes (such as *MEFV*, *TNFRSF1A*, *NLRP3* and *MVK*) but extended to a broad spectrum of more recently described autoinflammatory genes, reflecting the wide clinical heterogeneity of monogenic SAIDs. Several variants were significantly enriched in adults with Still's disease, including p.C81Y in *TNFRSF1A*, a well-established pathogenic variant in TNF receptor-associated periodic syndrome[190] that was identified in a patient with late-onset Still's disease-like symptoms, and *NLRC4* p.G786V, which was found in multiple patients with Still's disease and had previously been linked with periodic fever syndromes[191].

Importantly, many of the variants identified in this study are currently classified as variants of uncertain significance (VUS). Although not independently diagnostic, these VUS might act as genetic modifiers, lowering the threshold for autoinflammation when combined with environmental triggers, epigenetic changes or age-related somatic events. Indeed, putative somatic variants were found in ~30% of Still's disease cases[189], underscoring the contribution of postzygotic mosaicism to late-onset systemic inflammation.

Together, these findings support a model in which Still's disease arises from complex interactions between multiple rare germline VUS in monogenic SAID-associated genes and acquired somatic variants, converging on shared pro-inflammatory pathways such as IL-1 and IL-6 signalling. This framework not only helps to explain the variable and often late-onset phenotype of Still's disease but also highlights the blurred boundary between monogenic and polygenic autoinflammatory diseases.

Box 4 | Clonal haematopoiesis and somatic mosaicism in autoinflammatory disease

Somatic mosaicism — the presence of genetically distinct cell populations within an individual — is increasingly recognized as a ubiquitous phenomenon, especially within the haematopoietic compartment. Postzygotic mutations accumulate steadily throughout life, such that the haematopoietic stem cell (HSC) pool of a 70-year-old individual is estimated to carry more than one million protein-coding variants, corresponding to roughly one exonic mutation per HSC per decade[192]. Whereas most of these mutations are functionally silent, a minority confer a fitness advantage and drive age-related clonal haematopoiesis. This nearly universal process is associated with cardiovascular, metabolic, autoimmune and autoinflammatory comorbidities[189,193].

Within this context, loss-of-function variants in *TET2* represent a prototypical driver of clonal outgrowth. *TET2* mutations promote the expansion of altered myeloid progeny and dysregulated inflammatory signalling, thus creating a permissive background for disease[194]. Importantly, emerging data suggest that co-mutations in autoinflammatory genes (such as *NLRP3*, *NLRC4* and *MEFV*) can act as 'passenger' lesions, the phenotypic penetrance of which is amplified by TET2-driven expansion.

Several illustrative mosaic digenic models have been described:

- A patient with late-onset familial Mediterranean fever carried a mosaic *MEFV* variant restricted to myeloid cells, which co-segregated with a *JAK2* variant associated with secondary myelofibrosis[195].
- In cases of mosaic NLRC4- or NLRP3-driven autoinflammation, co-occurring *TET2* mutations provided a selective advantage for clonal expansion of inflammasome-primed myeloid cells[196,197].
- In VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, acquired *DNMT3A* and *TET2* variants frequently coexist with *UBA1* mutations, reinforcing both haematological and inflammatory manifestations[192,198].

Together, these examples highlight that the cellular genetic background — particularly the presence of clonal haematopoiesis-associated mutations such as *TET2* — can critically modulate the expressivity of mosaic autoinflammatory variants. This interplay provides a conceptual framework that links clonal haematopoiesis with late-onset or atypical presentations of autoinflammatory disease.

approaches that combine sequence information with structural and population-level data.

By incorporating 3D structural predictions from AlphaFold, new-generation tools such as AlphaMissense[15] can assess how a mutation perturbs folding, stability and molecular interactions in ways that traditional conservation-based scores cannot. This structural integration improves detection of context-dependent effects, including those occurring at allosteric sites or within regulatory domains, which are highly relevant for SAIDs[58]. Moreover, AlphaMissense demonstrates that combining structural insights with allele frequency data yields even greater accuracy[15], underscoring the value of multimodal assessments of variant pathogenicity. Together with AlphaMissense, PRESCOTT[14], VARITY_R (which is trained specifically on rare missense variants)[59], V2P[55] and ESM1b[60] rank among the most accurate multimodal predictors currently available for clinical variant classification[54]. Future analytical workflows could begin with broad genome-wide predictors such as CADD[61] for initial triage, followed by use of these specialized models to refine structural or mechanism-specific interpretation. This tiered strategy mirrors clinical practice, in which general screening tests are used to highlight potential concerns before more targeted assays provide mechanistic insight.

Challenges with structure-based methods

In the following subsections, we explore three complementary aspects of variant interpretation that expose the current limitations of structure-based approaches: protein stability prediction; the difficulties faced by in silico tools when analysing IDRs; and the specific challenge posed by GoF variants. Together, these perspectives help to define the next step towards precision medicine in SAIDs.

Predicting the effects of mutations on protein stability. Protein stability — commonly expressed as the change in Gibbs free energy ($\Delta\Delta G$) upon mutation — has long been recognized as a crucial link between missense variants and deleteriousness. Many pathogenic variants destabilize proteins, thereby impairing folding, structural integrity or solubility[62,63]. Computational tools such as FoldX[64], Rosetta[65] and DynaMut[66] estimate these stability changes using physical models of protein structure. These approaches are most effective for well-structured protein domains for which high-resolution 3D models are available. Yet changes in $\Delta\Delta G$ alone are neither necessary nor sufficient to explain pathogenicity.

Large-scale analyses have shown that a substantial fraction of disease-associated variants fall within a moderate destabilization range (that is, 2–4 kcal/mol), which overlaps considerably with the range observed for many benign variants[67]. These observations suggest that pathogenicity often stems from subtle destabilizing effects. Many proteins, including those involved in SAIDs, naturally operate near their folding limits; thus, even small perturbations can tip the balance towards misfolding, aggregation or rapid degradation[68]. To date, comprehensive $\Delta\Delta G$ analyses have not been performed for putative LoF variants in SAIDs, although isolated studies (for example, of *TNFAIP3* variants identified in people with haploinsufficiency of the ubiquitin-editing enzyme A20) have applied stability calculations to predict the damaging effect of specific mutations[69].

MuLAN[70], a deep-learning model trained directly on experimental ΔΔG measurements and their correlations with LoF variants and relying solely on protein sequences using protein language models, was applied to 13 GoF variants in SAID-associated genes, including *MEFV* and *NLRP1*. As described in the preprint available in bioRxiv[70], MuLAN consistently outperformed AlphaMissense, highlighting the value of stability-informed models for GoF predictions.

Specific biophysical properties, cellular roles and regulatory environments of individual proteins add further complexity. Highly expressed proteins or those under strict quality-control mechanisms are more sensitive to destabilizing change[71]. Conversely, IDR-containing proteins (see below) can often tolerate greater biophysical perturbations without causing disease[72]. Consequently, $\Delta\Delta G$ thresholds for pathogenicity are not universal but depend on each protein's

specific biophysical and cellular environment as exemplified by the temperature-sensitive destabilization of mevalonate kinase (discussed further below). Moreover, cellular mechanisms, such as molecular chaperones and proteasomal degradation pathways, further influence the clinical effect of destabilizing variants[73]. Two variants with identical $\Delta\Delta G$ values can therefore result in markedly different disease phenotypes depending on the proteostasis landscape of the affected tissue.

In the past 5 years, deep-learning models specifically designed to improve predictions of $\Delta\Delta G$ caused by missense variants[74] have emerged. Among them, DDMut[75] performs well for both destabilizing and stabilizing variants, overcoming a limitation of many earlier tools. Although DDMut does not directly classify variants as pathogenic, it offers precise mechanistic estimates of effects on stability, which can be incorporated into broader predictive pipelines alongside models such as AlphaMissense or PRESCOTT. DDMut surpasses the performance of earlier tools such as DynaMut, which was previously used to study a cold-responsive NLRP3 variant (p.L413V) implicated in autoinflammatory disease[29]. Structure-based methods such as DDMut are generally preferred when a reliable 3D model is available, as they capture local structural and energetic contexts that are critical for accurate ΔΔG prediction. However, sequence-based methods (such as SPIRED-Fitness[76] or MuLAN), which are based on protein language models, become essential in settings in which structural information is absent or uncertain – for instance, in IDRs or proteins without confident

Table 1 | In silico protein predictors for human variant classification

Model type	Tool(s)	Data sources	Description	Refs.
Established computational predictors				
Supervised machine learning	PolyPhen-2, SIFT, VARITY, MutPred2	Curated variant labels, evolutionary conservation, protein sequence features	Trained on curated, clinically classified variants to recognize features associated with pathogenicity, such as conservation through evolution	59,171–173
Structure-based models	FoldX, mCSM, Rosetta	Protein 3D structures, energy terms, conformational data	Use protein 3D structure to estimate whether mutations destabilize folding or disrupt key conformations	64,65,174
Structure–dynamics models	DynaMut	Protein 3D structures, normal mode dynamics, residue environment features	Combines normal mode dynamics with graph-based structural features to predict the effect of mutations on protein stability and flexibility	66
Genome-wide annotation models (unsupervised or semi-supervised)	CADD	Genomic annotations (evolutionary conservation, regulatory features, chromatin marks), population variation	Integrates diverse genomic annotations to contrast observed variants in healthy populations with simulated variants, scoring those rarely tolerated by evolution as more likely to be pathogenic; independent of clinical labels or structural data	61,92
Ensemble meta-predictors	REVEL	Predictions from multiple existing tools	Combines outputs from multiple tools to improve robustness (akin to getting several medical opinions)	52,175
Emerging deep-learning and integrative models				
Protein language and generative models (unsupervised DL)	EVE, ESM1b, and other models in ProteinGym benchmarks	Multiple sequence alignments, single protein sequence, structure	Systems reconstructing complete protein mutational landscapes across species; learn the 'grammar' of proteins from sequences/MSA; enable variant effect prediction across proteins without clinical labels	60,176
DL integrative pathogenicity predictors	AlphaMissense, PrimateAI, PrimateAI-3D	Sequence, structure, population allele frequency; human and primate variations	Supervised and semi-supervised DL models integrate multiple evidence types to predict missense pathogenicity; PrimateAI-3D adds 3D structural context	15,175
DL protein stability and fitness predictors	DDMut, SPIRED-Fitness	Experimental or AlphaFold2 protein structures, evolutionary conservation, graph neural networks, DMS data, single-sequence predictors	DL approaches focused on biophysical stability (ΔΔG) or mutational fitness; SPIRED-Fitness predicts both structure and variant fitness in one model	75,76
Epistatic and structural integrative models	PRESCOTT	MSA, structure, population allele frequency	Models evolutionary conservation, epistasis and structure (with or without population data) to capture combined residue effects	14
Sequence-based DL interaction predictors	MuLAN	Protein sequences (variants and binding partners), protein language model embeddings	DL model predicts variant effects on protein–protein interactions and binding affinity from sequences alone	70

ΔΔG, change in Gibbs free energy; DL, deep learning; DMS, deep mutational scan; MSA, multiple sequence alignments.

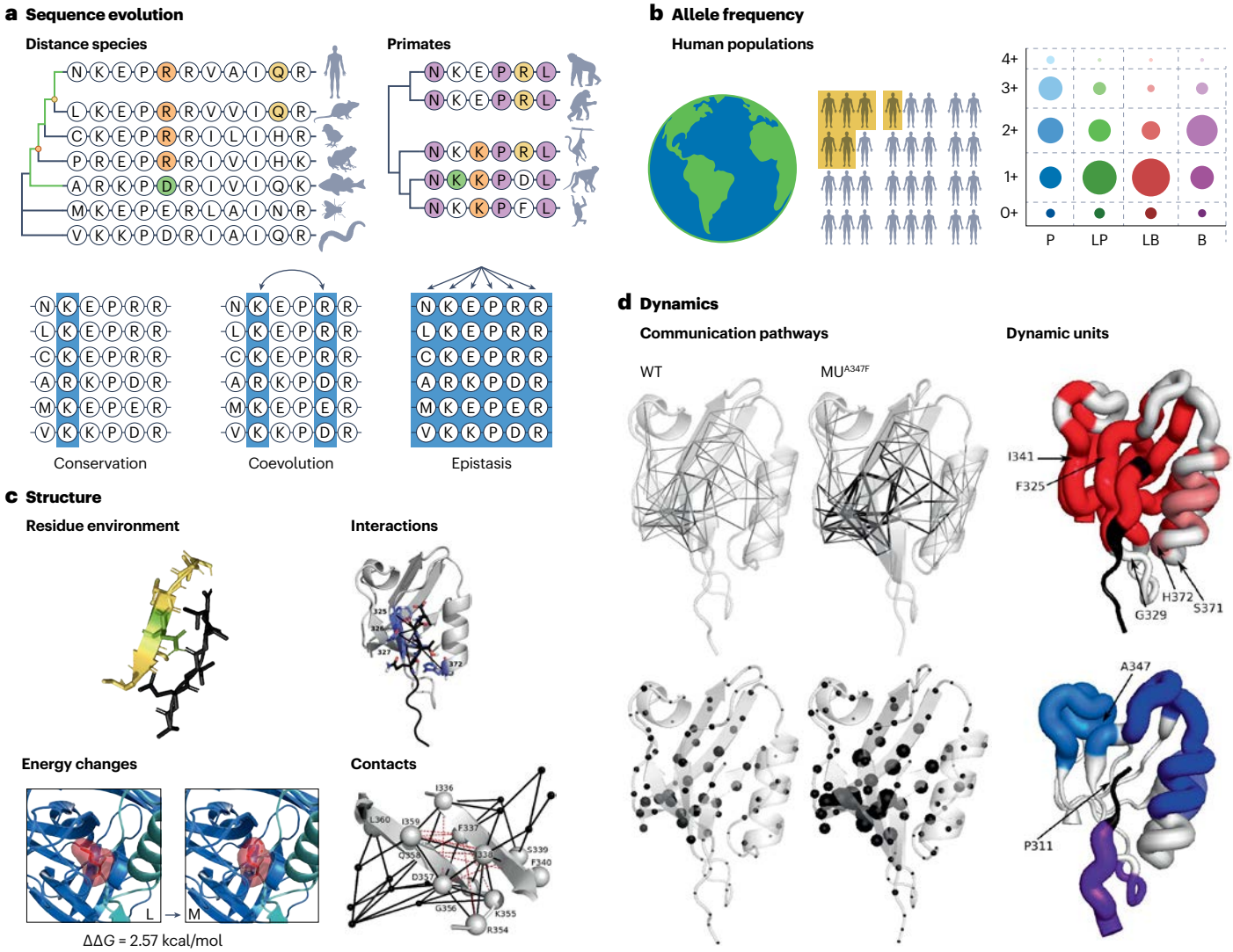

Fig. 1 | Data sources used by in silico predictors to distinguish pathogenic from benign variants. The information exploited by current predictors to infer whether a missense variant is pathogenic or benign can be broadly grouped into four categories: evolutionary conservation, population allele frequency, structural stability and dynamics based. **a**, Sequence-derived features include evolutionary conservation scores for individual positions, coevolution signals between residue pairs, and epistatic effects emerging from the contextual landscape of amino acid substitutions. **b**, Allele frequency data are collected from healthy populations and/or patient cohorts and provide insight into the tolerance or intolerance of specific genes to variation. Variants are classified pathogenic (P), likely to be pathogenic (LP), benign (B) or likely to be benign (LB), and 0+–4+ refers to the review status (that is, the level of review supporting the variant classification) in ClinVar. Circle size schematizes the number of annotated missense variants for each combination of clinical classification and review status. **c**, Structural features are obtained from experimental structures or structural models, covering the local environment of the residue, interaction interfaces with ligands (proteins, nucleic acids or small molecules), variant-induced energy changes and residue–residue contacts. $\Delta\Delta G$, Gibbs free energy. **d**, Dynamics-based data, derived from short- or long-timescale simulations, capture differential atomic fluctuations between the wild type (WT) and mutant (MU) states. Illustrations of conservation, coevolution and epistasis models are adapted from ref. 177, Springer Nature; energy changes image is reproduced from ref. 70, CC-BY-NC 4.0 (https://creativecommons.org/licenses/by-nc/4.0/); and interactions, contact, communication pathways and dynamic units images are reproduced from ref. 178, CC-BY 4.0 (http://creativecommons.org/licenses/by/4.0/).

experimental or AlphaFold models – as they leverage evolutionary and coevolutionary signals directly from protein sequences.

The challenge posed by intrinsically disordered regions. A major limitation of most structure-based and conservation-based models for variant effect prediction is their poor performance in IDRs[77]. This gap is a critical one, as IDRs constitute more than 40% of the human proteome and more than half of human proteins contain a combination of folded domains and disordered segments[78,79]. Unlike structured domains that adopt a stable 3D conformation, IDRs are flexible and

dynamic. Yet they are essential for a wide range of functions, notably by mediating protein–protein interactions[77]. For instance, *MEFV* exon 2 encodes a long IDR linker (Supplementary Fig. 1) that contains the two key serine residues controlling pyrin inflammasome activation through phosphorylation–dephosphorylation cycles and causing pyrin-associated autoinflammation with neutrophilic dermatosis when mutated[80,81].

Beyond their roles in protein–protein interactions, IDRs contribute substantially to liquid–liquid phase separation (LLPS), a process that drives the assembly of biomolecular condensates that can act as supramolecular organization centres to trigger immune signalling[82]. Although the link between VUS and LLPS in SAIDs has not been systematically explored, LLPS has well-characterized roles in the assembly and activation of the NLRP3 and NLRP6 inflammasomes[83,84].

Mutations within IDRs are implicated in 20–50% of genetic diseases[72,85]. However, most widely used computational models (including those listed in Table 1) were not designed to account for IDRs and their accuracy in distinguishing pathogenic from benign variants within IDRs is thus limited. Improving variant classification in these regions will probably require explicit integration of disorder-specific features and moving beyond the traditional static structure–function paradigm towards frameworks that capture the biophysical properties of dynamic protein regions[85,86].

The challenge posed by gain-of-function variants. A fundamental limitation of most current tools for the classification of variants is their implicit bias towards detecting LoF variants[87]. LoF variants typically destabilize the protein structure, disrupt active or binding sites, or abolish essential interactions – effects that structure-based models can often capture by estimating destabilization energies or by identifying disrupted interaction hotspots[88]. By contrast, GoF variants, which can enhance enzymatic activity, introduce new molecular functions, or inappropriately activate signalling pathways, and which represent a substantial proportion of monogenic SAID-associated variants (Supplementary Table 1), remain far more challenging to identify[89]. Many GoF mechanisms are subtle[88], acting through long-range allosteric effects, altered regulatory dynamics, or post-translational modifications, none of which necessarily destabilize the protein or leave strong evolutionary conservation signals. As a result, tools predominantly tuned to detect LoF phenotypes often fail to recognize these clinically important variants.

Emerging approaches are beginning to address this knowledge gap and show a measurable advantage over previous tools in detecting GoF variants, particularly in regulatory and autoinflammatory genes. A 2025 analysis[14] of a dataset of well-established GoF variants across 13 human genes implicated in SAIDs and IEIs demonstrated the limitations of existing predictors, with average rates of correct classification of pathogenic GoF variants ranging from 74.5% down to 42% depending on the computational method used. Notably, most *MEFV* GoF variants were misclassified as benign.

Structural analyses[58,88] show that GoF variants often cluster in regulatory or allosteric regions, rather than catalytic cores, emphasizing the need for predictive models that go beyond traditional stability-based or conservation-based metrics. Striking differences have also been observed between recessive and dominant, as well as LoF and non-LoF, variants: dominant non-LoF variants typically have milder effects on protein structure and are highly enriched at protein interfaces[88]. These non-LoF variants often cluster in 3D space, suggesting that spatial localization patterns could help to distinguish them.

Together, these findings highlight the opportunity to improve variant prediction by incorporating molecular disease mechanisms, regulatory architecture and structural context into computational frameworks. At present, however, no widely used predictors explicitly distinguish between GoF and LoF effects, underscoring a critical shortcoming of current tools.

Benchmarks for computational prediction

Validation of computational predictions is essential to establish the validity of a new technique and relies on either clinical databases (such as ClinVar or Infevers) or experimental data. Benchmarking computational approaches with clinical annotations have been used to redefine the thresholds of computational methods and improve the discrimination between benign and pathogenic variants either globally[54] or even on a single-gene basis, as exemplified by the use of REVEL to improve the classification of *MEFV* variants[90]. Regarding experimental validation, MAVE[16] experiments, including deep mutational scans (DMS), systematically measure the functional effect of thousands of mutations and have provided large experimental datasets for benchmarking computational predictions. The ProteinGym database, available online[91], is a collection of benchmarks encompassing over 250 DMS assays. ProteinGym enables rigorous comparisons of computational predictions and biological assays and provides a reference framework for assessing computational prediction accuracy[92]. Although ProteinGym includes clinically important proteins such as p53 and BRCA1, it currently lacks coverage of proteins driving SAID pathogenesis (such as NLRP3 or mevalonate kinase), indicating that the specificities of SAID-associated VUS cannot be tested using this benchmark database. Encouragingly, DMS studies of *NLRP3, MEFV* and *ADA2*, each encompassing >100 missense variants, have now been reported[29,93,94]. Similarly, a study based on saturation genome editing[4] was performed for CARD11, an adaptor protein with variants linked to IEIs, covering 2542 coding variants[5], and a study on the IEI-associated genes *PIK3CD* and *PIK3R1* supported the classification of >100 variants[95]. These landmark experiments provide a foundation for incorporating SAID- and/or IEI-associated proteins into future benchmarking efforts.

Decoding variants of uncertain significance via functional tests

Although in silico prediction has advanced considerably in the past 10 years (particularly for LoF variants), functional testing remains the gold standard for determining the effects of VUS and classifying them as neutral, hypomorphic or hypermorphic. Approaches range from in vitro testing of recombinant protein variants to in vivo testing in animal models.

Studying pathogenic variants in SAIDs (and in general in IEIs) requires tailored functional tests. With the exception of a few nonsense or frameshift variants with obvious LoF consequences, a diversity of mechanisms can result in hypomorphic variants. Similarly, hypermorphic variants involve a spectrum of GoF mechanisms ranging from constitutive activation (for example, specific somatic *NLRP3* variants) to disruption of regulatory mechanisms (such as the loss of the caspase-8 cleavage site in the case of cleavage-resistant RIPK1 (ref. 96)). Missense variants can also be neomorphic (conferring novel function to the corresponding protein variant), as exemplified in the case of ROSAH syndrome-associated *ALPK1* variants, which shift ALPK1 activity from recognizing exclusively non-self microbial molecules to sensing endogenous molecules and triggering autoinflammation[97] (Fig. 2). Through specific SAID examples, we highlight the

diversity of methods and the key challenges associated with functional VUS testing.

Decoding variants of uncertain significance through in vitro tests

In a few cases, when the mutated gene encodes an enzyme, the effect of a mutation can be tested directly by purifying the corresponding recombinant protein and measuring its activity. Mevalonate kinase deficiency (MKD) corresponds to a continuum of autoinflammatory diseases ranging from mild forms (previously termed hyper IgD and periodic fever syndrome) to severe presentations (previously termed mevalonic aciduria). Assaying the enzymatic activity of distinct mevalonate kinase variants has revealed a range of activity, from near-complete loss (<2%) to partial loss of specific enzyme activity (for instance, ~50% for the *MVK* p.V261A variant)[98–100]. Unlike cellular assays, in which residual mevalonate kinase activity in a patient's cells correlates with the clinical phenotype (<0.5% of the normal level of activity in mevalonic aciduria and 1–7% in mild MKD)[98,101], the specific activity of the different recombinant isoforms does not enable a genotype-to-phenotype classification. This discrepancy probably reflects the contribution of additional cellular processes, such as misfolding and/or destabilization of the corresponding proteins in the intracellular environment and proteasome-mediated degradation, highlighting the need to validate the effect of VUS in a cellular context.

Similarly, deficiency of adenosine deaminase type 2 (DADA2) is an autosomal-recessive disease caused by LoF variants in *ADA2* (refs. 102,103). This disease, initially reported in patients with systemic inflammation, polyarteritis nodosa (a systemic necrotizing vasculitis), strokes and livedo racemosa, can be associated with a broad spectrum of immunodeficiencies and haematological and autoinflammatory manifestations[104]. ADA2 is a secreted enzyme and quantification of ADA2 activity in the plasma of patients is used to validate DADA2 diagnoses and the pathogenicity of *ADA2* variants[102,103]. Sixty-three ADA2 missense variants identified in people with DADA2 were also tested for their enzymatic activity upon ectopic expression in human embryonic kidney (HEK)-293 cells, and 87% of the variants showed <25% residual enzymatic activity compared with wild type ADA2 (ref. 94), enabling the validation of their pathogenicity while also demonstrating a continuum of phenotypes ranging from variants with undetectable activity to variants with >60% residual activity. Interestingly, 30 of the 100 most frequent *ADA2* variants in gnomAD (including 15 DADA2-associated variants) also displayed <25% enzymatic activity, indicating that they are hypomorphic variants[94]. Given the allele frequency of

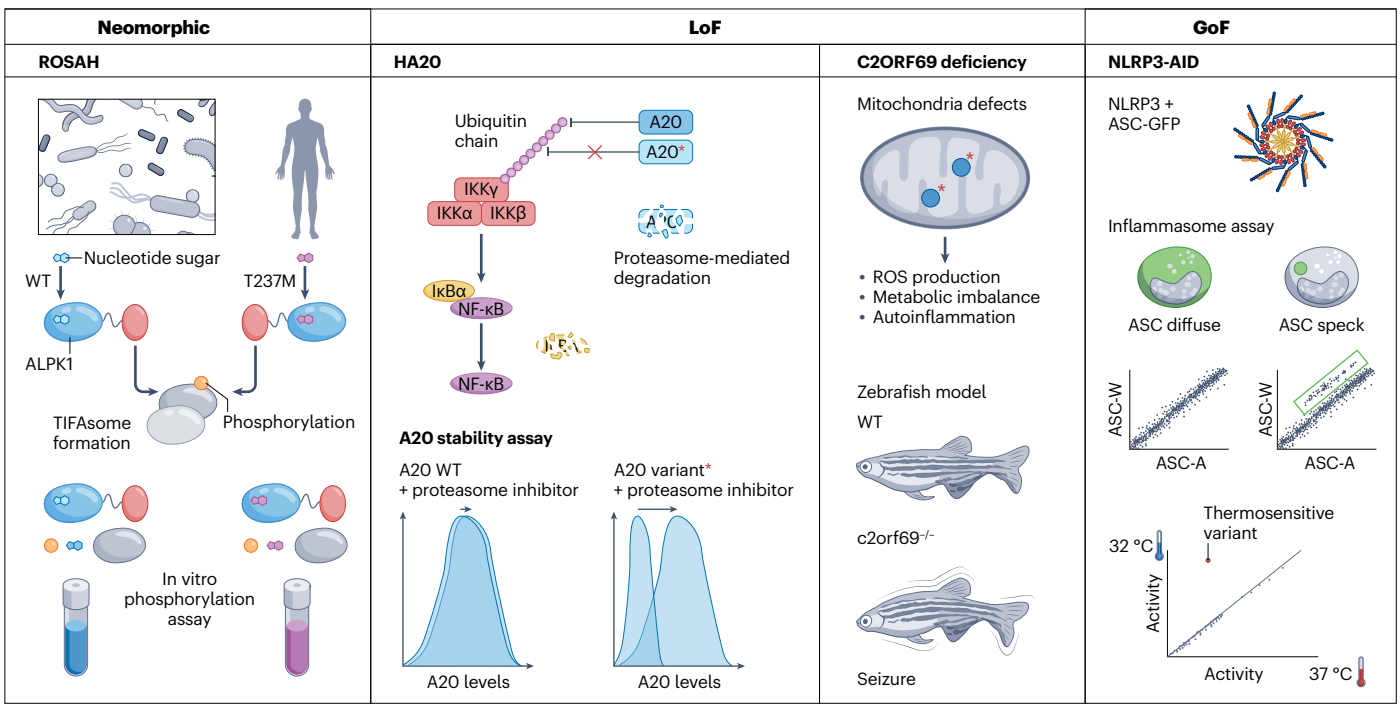

Fig. 2 | Selected examples of pathogenic mechanisms in systemic autoinflammatory diseases and associated variants of uncertain significance-characterizing techniques. The neomorphic p.T237M variant of ALPK1 observed in ROSAH syndrome is illustrated in the left panel. 'Wild type' (WT) ALPK1 senses only bacterial nucleotide sugars, whereas the p.T237M ALPK1 variant responds to self (human) nucleotide sugars. Activation of ALPK1 leads to phosphorylation of TIFA and TIFAsome formation. In vitro phosphorylation assay with recombinant proteins is used to assess the pathogenicity of variants of uncertain significance (VUS). Two loss-of-function (LoF)-associated diseases are illustrated in the central panels: haploinsufficiency of A20 (HA20) and C2ORF69 deficiency. In HA20, the deubiquitinase A20 protein is destabilized, degraded in a proteasome-dependent manner and rendered unable to inhibit NF-κB activation. Flow cytometry is used to monitor A20 VUS protein levels in the presence or absence of proteasome inhibitors. C2ORF69 deficiency is associated with mitochondrial dysfunction, an increase in reactive oxygen species (ROS) production and an imbalance in metabolism, resulting in autoinflammation. *C2orf69*$^{-/-}$ zebrafishes present with seizures, a symptom also observed in human patients. The right panel illustrates NLRP3 gain-of-function (GoF) VUS observed in NLRP3-associated autoinflammatory disease and the flow cytometry technique used to monitor inflammasome activation through the visualization of ASC-eGFP speck formation. Performing assays at 37°C and 32°C enables the identification of thermosensitive variants.

these hypomorphic variants, it is estimated that there are more than 30,000 people with DADA2 worldwide[94].

Decoding variants of uncertain significance through in cellulo tests

Most functional assays on VUS are performed in cellulo using ectopic expression systems. A precise understanding of the signalling pathways involved and the choice of an appropriate cell type are essential to obtain robust functional assays.

Developing a functional assay. HEK-293 cells are widely used in in cellulo tests owing to their high transfection rate. These cells can be easily co-transfected with reporter- and VUS-encoding plasmids. For example, NF-κB luciferase reporter assays in HEK-293 cells have enabled the identification of hypermorphic variants in *ALPK1* and *NOD2* associated with ROSAH[97,105–107] and Blau[108] syndromes, respectively, as well as hypomorphic variants in *RNF213* linked to urticarial lesions with hypercytokinaemia[109]. Studies using these assays demonstrated that HEK-293 cells express the innate immune proteins required for the tested pathway (for example, TIFA–TRAF6 in the ALPK1 pathway[97,105–107], RIPK2 downstream of NOD2 (ref. 108), or CYLD, a negative regulator of the NF-κB pathway targeted by the ubiquitin ligase RNF213 (ref. 109)). Yet these cells lack inflammasome proteins. Thus, functional assays of inflammasome variants in HEK-293 cells require co-transfection with plasmids encoding inflammasome proteins, notably ASC, the inflammasome adaptor protein. ASC speck formation, which is detectable by microscopy or flow cytometry, serves as a surrogate marker for inflammasome activation and enables high-throughput assays[110]. HEK-293 cells expressing ASC–GFP fusion protein have been used to characterize hypermorphic variants in inflammasome sensors (for example, *NLRP1* in multiple self-healing palmoplantar carcinoma, familial keratosis lichenoides chronica syndromes and NLRP1-associated autoinflammation with arthritis and dyskeratosis[111–113]; NLRP3 in *NLRP3*-associated autoinflammatory disease[14]) (Fig. 2), as well as hypomorphic variants in negative regulators (such as *DPP9* variants that fail to restrain NLRP1 and CARD8 inflammasomes[114,115]).

Nevertheless, these cells cannot serve as a universal system. For instance, pyrin-associated autoinflammation with neutrophilic dermatosis-associated *MEFV* variants are hypermorphic when transfected into HEK-293 cells, whereas most FMF-causing *MEFV* variants (such as p.M694V) behave like wild type *MEFV* in this system, indicating that caution is needed when interpreting negative results[80]. Cell lines more relevant to the disease aetiology than HEK-293 cells are preferable, including THP1 or U937 monocyte-like cells for *NLRP3* or *MEFV*[30,93,116], keratinocytes for *NLRP1* (ref. 111) or DT-40 B cells for *PLCG2* studies[117]. Expression profiling databases (such as Dice or Human Protein Atlas) can guide rational selection of cell models for genes that are not ubiquitously expressed[118,119].

Decoding of VUS can also be performed directly on patient-derived cells (for example, peripheral blood mononuclear cells or monocytes) once the pathological mechanisms and the appropriate ex vivo conditions to reveal dysfunction have been established[30,120,121]. Yet obtaining definitive proof of pathogenicity can be challenging, as inter-individual variability often exceeds the effect of pathogenic variants. Primary skin fibroblasts can be used as an alternative to blood cells whenever the studied pathway is not restricted to myeloid cells. For example, fibroblasts from a patient with disabling pansclerotic morphea, a rare and severe SAID characterized by poor wound healing and fibrosis and associated with *STAT4* GoF variants, were used to demonstrate a wound-healing defect in a scratch assay as well as increased IL-6 production at steady state[122]. Induced pluripotent stem cells (iPSCs) are an appealing model, especially when blood cells are not available for functional assay. iPSCs derived from a patient with haemophagocytic lymphohistiocytosis (HLH)-like hyperinflammation were used to demonstrate a deleterious reduction in DPP9 protein levels[114]. iPSCs are amenable to CRISPR–Cas9-mediated gene correction, enabling evaluation of the effect of a missense mutation, and its correction, within the specific genetic context of the patient. Such experiments in iPSC-derived macrophages have been instrumental in demonstrating the role of IFN-γ priming in the NF-κB hyperactivation mediated by *NOD2* variants in Blau syndrome. Specifically, IFN-γ induces NOD2 expression, leading to a pathological expression of the Blau-causing *NOD2* variant, a phenomenon not observed in steady-state ex vivo conditions[123]. Similarly, iPSC-derived endothelial cells and genetically corrected isogenic cells were generated from a patient presenting with cutaneous vasculitis to demonstrate the effect of the *LYN* GoF variant present in the patient on endothelial immune activation and on neutrophil transendothelial migration[124].

Controlling the level of ectopic expression is essential for demonstrating functional dysregulation of variants. In the case of *ALPK1* (ROSAH syndrome) or *NOD2* (Blau syndrome) variants, enforced expression reveals dysregulations that are difficult to detect in primary cells from patients[107,108]. Conversely, enforced expression of wild type inflammasome sensors can trigger constitutive inflammasome activation in the absence of activating stimuli[125], underscoring the need to tightly control the expression level of variants in order to distinguish hypermorphic variants from wild type-like variants. As mentioned above, inflammasome activation can be quantified at the single-cell level by assessing ASC speck formation using flow cytometry. This readout can be combined with simultaneous measurement of inflammasome sensor expression by incorporating fluorescent translational fusions (for instance, NLRP3–T2A–mCherry, in which the T2A ribosomal skipping sequence ensures equimolar production of NLRP3 and mCherry)[29,110,126].

The development of robust functional assays therefore requires a detailed understanding of the molecular pathways involved, with specific tests tailored to hypomorphic and hypermorphic VUS.

Decoding loss-of-function and hypomorphic variants. The spectrum of LoF variants extends far beyond premature stop or frameshift variants and, as presented below with the example of *TNFAIP3* variants, sophisticated assays are sometimes necessary to demonstrate the hypomorphic nature of variants.

TNFAIP3 encodes the ubiquitin-editing enzyme A20, a negative regulator of the NF-κB pathway. Whereas the wild type A20 protein is stable (half-life >24 h), the half-life of the pathogenic missense variant p.L264P is <3 h owing to misfolding and proteasome-mediated degradation. Sensitivity to proteasome-mediated degradation has therefore been exploited to develop functional assays; for example, to quantify A20–GFP fusion proteins in the presence or absence of proteasome inhibitors[69] (Fig. 2). More-refined dual fluorescent reporter systems that link the protein of interest to one fluorophore and co-express a second fluorophore in equimolar amounts enable protein stability to be quantified by flow cytometry, with or without proteasome inhibition, and can be scaled up for many variants[127,128].

The complexity of interpreting hypomorphic variants can be illustrated by a rare *TNFAIP3* allele consisting of p.T108A and p.I207L missense substitutions, which is found in healthy individuals from

Southeast Asia and Oceania and traces back to *Denisova hominins*, an extinct species distantly related to Neanderthals[129]. This hypomorphic variant increases TNF response and modestly reduces NF-κB inhibition but does not cause spontaneous autoinflammatory disease in humans or mice; instead, it is associated with improved survival following coxsackievirus infection[129]. Among a continuum of variants with graded effects, determining the threshold between a beneficial fine-tuning of inflammation (possibly associated with positive selection) and a deleterious effect is very challenging. Accordingly, although in vitro assays can classify VUS as hypermorphic, neutral or hypomorphic, the integration of clinical data remains essential to establish pathogenicity.

The specific case of dominant-negative variants. Functional tests are particularly important in cases in which the inheritance pattern of a variant does not align with the known mode of inheritance of the associated disease.

OTULIN-related autoinflammatory syndrome (ORAS, also termed otulipenia) is a severe autoinflammatory syndrome caused by biallelic LoF or hypomorphic variants in *OTULIN*. *OTULIN* encodes a deubiquitinase that antagonizes the linear ubiquitinated chain assembly complex involved in NF-κB activation[130]. ORAS-associated *OTULIN* variants include those that introduce a premature stop codon, decrease OTULIN stability, or affect its ubiquitin binding pocket[130,131]. Although ORAS is classically considered a recessive disease, three patients each carrying a single de novo variant (p.R306Q or p.C129S) were identified. Functional assays following co-transfection of the pathogenic and wild type variants revealed that these variants act in a dominant-negative manner[132,133]. At the molecular level, the mechanism of the p.R306Q variant remains unclear, whereas the p.C129S variant is catalytically dead but has a high ubiquitin chain-binding affinity that probably outcompetes wild type *OTULIN*, thus shifting the ubiquitination–deubiquitination balance towards accumulation of ubiquitin chains. Interestingly, *OTULIN* haploinsufficiency has been reported in patients who developed severe TNF-mediated inflammatory syndromes following infections, surgical interventions or unknown environmental triggers, with variable penetrance[134–136]. These observations suggest that decoding *OTULIN* VUS could have important implications beyond SAIDs and illustrate the continuum between SAIDs and primary immunodeficiencies.

In addition to *OTULIN*[132,133], dominant-negative variants that cause distinct SAIDs have been described in *RELA*[137], *NFKBIA* (encoding IκBα))[138], *DPP9* (ref. 114), *PLCG2* (ref. 117), and *ADA2* (refs. 139,140).

Intracellular protein localization. Interpreting the effect of certain VUS requires assessment of the intracellular localization of the corresponding proteins. Variants in *CDC42* are linked to diverse neurodevelopmental phenotypes collectively known as Takenouchi–Kosaki syndrome. Interestingly, variants affecting the C-terminus of CDC42 cause a distinct condition associated with dyshaematopoiesis, inflammation and HLH and is referred to as neonatal-onset cytopenia, autoinflammation, rash and HLH (NOCARH) syndrome[141]. The C-terminus of CDC42 undergoes isoprenylation (the addition of a lipid group, enabling targeting of CDC42 to the plasma membrane); variants affecting this region can disrupt this post-translational modification, resulting in protein mislocalization. Notably, the CDC42 p.R186C mutation introduces a cysteine residue that is palmitoylated, resulting in redirection of CDC42 to the Golgi. This aberrant localization activates the pyrin inflammasome[142], triggers STING hyperactivation and endoplasmic reticulum stress[143], and ultimately results in a SAID distinct from Takenouchi–Kosaki syndrome. This example illustrates how different variants of a given gene can give rise to distinct diseases.

Decoding variants of uncertain significance in animal models

Most pathogenic missense variants affect residues that are highly conserved across species. This property has been exploited for in silico prediction and provides opportunities to functionally test variants in diverse animal models, including non-vertebrates.

Caenorhabditis elegans (a small worm) has been used to characterize the effect of *CDC42* VUS on developmental processes. The comparison of two NOCARH syndrome-associated variants (p.R186C and p.C188Y) with wild type CDC42 in this model revealed hypomorphic effects on vulval development[141,144]. However, as *C. elegans* lacks the cGAS–STING pathway and inflammasomes, the consequences of these variants for innate immunity cannot be investigated in this animal. Other simple organisms, including flies (*Drosophila melanogaster*) and zebrafish (*Danio rerio*) have been used to study *PLCG1* (ref. 145), *TNFAIP3* (ref. 146), *UBA1* (ref. 44) and *C2Orf69* (ref. 147) VUS (Fig. 2), highlighting the utility of such models for rapid functional assessment.

By contrast, mouse models remain the gold standard owing to their closer resemblance to the human immune system. Multiple mouse models of autoinflammatory diseases have been developed, providing valuable preclinical tools. For instance, a transgenic mouse expressing the FCAS-associated NLRC4 variant p.H443P exhibited constitutive autoinflammation, and exposure to cold further exacerbated inflammation, recapitulating the cold-induced symptoms observed in patients with FCAS[37].

Nonetheless, animal models present challenges owing to the absence of orthologues in rodents (as in the case of *ADA2* (refs. 148,149)) or to sequence divergence between human and murine orthologues. For example, murine pyrin contains a premature stop codon, resulting in the production of a protein that lacks the B30.2 domain in which most FMF-causing mutations cluster. To overcome this structural difference between murine and human pyrin, three FMF-associated variants (p.M680I, p.M694V and p.V726A) were introduced into a knock-in mouse expressing a chimeric pyrin protein with the human B30.2 domain. These mice developed systemic inflammation, although the severity of disease correlated inversely with that in humans (for example, the p.V726A variant that is associated with a mild FMF phenotype in humans causes severe disease in mice)[150].

Of note, several pathogenic variants (such as NLRC4 p.V341A and PSTPIP1 p.A230T, among others) fail to cause autoinflammatory disease in mice[151–154], underscoring the difficulty of interpreting negative data in animal models.

Variants of uncertain significance and environmental modulators

SAIDs most often progress through recurrent inflammatory flares, suggesting that, in addition to genetic factors, endogenous or exogenous triggers can act as initiators of these flares. Taking into consideration these triggers when testing VUS can be important, as exemplified with temperature.

Cold-induced urticaria can be directly assessed in patients using ice-cube application or cold-water immersion. Interestingly, some people with SAIDs test negative with use of these methods but show positive responses to skin testing with evaporative cooling, underscoring the need for specific diagnostic tests[155]. These patients often present with VUS in *PLCG2*, which encodes phospholipase Cγ2 (PLCG2), an

Glossary

Benchmarking
The systematic comparison of different prediction methods using standardized datasets to evaluate their performance under the same conditions.

Biallelic
Refers to the presence of variants in both alleles of a gene, one inherited from each parent, that is required for the expression of recessive traits or diseases.

De novo
Describes a new genetic change appearing for the first time in a patient, not inherited from either parent.

Deep learning
An advanced type of machine learning that uses many layers of interconnected 'neurons' to automatically learn complex patterns from large datasets, capturing relationships too subtle for simpler methods.

Dominant-negative
A type of mutation in which the altered gene product negatively interferes with the normal function of the gene product of the non-mutated allele.

Epistatic interactions
Genetic interactions in which the effect of a variant depends on the presence of one or more other variants, meaning their combined effect is not simply the sum of their individual effects.

Gain of function
(GoF). Describes a genetic variation that increases the activity of the gene product, sometimes leading to disease.

Haploinsufficiency
A situation in which one functional copy of a gene is not sufficient to produce the normal amount of gene product needed for healthy function, so loss of one allele leads to disease.

Hypermorphic
Describes a gain-of-function variant that enhances the activity of the corresponding protein.

Hypomorphic
Describes a variant that decreases the activity of the corresponding protein.

Loss of function
(LoF). Describes a genetic variation that reduces or abolishes the activity of the gene product, sometimes leading to disease.

Multiplexed assays of variant effect (MAVE) experiments
Functional assays of large libraries of variants that establish, in a single experiment, a score-based classification of all the variants in terms of activity.

Penetrance
Describes the proportion of individuals with a specific genetic variant who express the associated phenotype (such as symptoms of the disease).

Protein language model
A deep-learning model trained on large protein sequence datasets that learns patterns in amino acid order to generate representations enabling prediction of structural and functional properties.

Saturation genome editing
CRISPR-based method that systematically introduces all possible single-nucleotide variants within a specific coding sequence.

Segregation analysis
The study of how a variant is inherited within families to assess whether it co-occurs with disease.

Somatic variant
Genetic variant that occurs in non-germline cells after conception; it is acquired during a person's lifetime and is not inherited.

enzyme highly expressed in B cells that promotes ERK phosphorylation and calcium flux upon B cell receptor engagement. B cells transfected with cold-induced urticaria-associated PLCG2 variants display GoF activity at 20°C, whereas at 37°C PLCG2 activity is either unchanged or even reduced[155]. Since this initial discovery, additional PLCG2 variants with hypermorphic behaviour at 37°C have been identified in patients without cold-induced urticaria, further highlighting both the complexity of VUS functional testing and the importance of incorporating clinical features into the design of functional assays[117].

Cold-induced inflammation is also observed in a subset of patients with CAPS, hence the original name of NLRP3, cryopyrin[156]. Functional studies have identified several NLRP3 variants that demonstrate increased activity at 32°C, many of which are associated with FCAS, demonstrating good concordance between functional tests and clinical phenotypes[29]. Similarly, certain *NLRC4* variants linked to FCAS promote enhanced IL-1β release at 32°C compared with at 37°C[37].

By contrast, the *MVK* variants p.V377I and p.A148T encode enzymes that are stable at 30°C but become destabilized at 37°C and even more so at 39°C. These findings suggest that febrile attacks could act as a trigger or amplifier of inflammation in patients with MKD carrying one of these variants[157].

Other endogenous modulators such as metabolites can also specifically regulate the activity of some variants. Indeed, progesterone and testosterone catabolites can regulate the pyrin inflammasome[158], and some *MEFV* variants confer a 100-fold higher sensitivity to these catabolites than wild type *MEFV*[159]. The functional relevance of these metabolites in pyrin-associated autoinflammatory diseases remains to be demonstrated but they could explain menstruation-associated inflammatory flares in female patients with FMF[160].

Of note, functional assessment of VUS is still predominantly supported by research infrastructures rather than embedded in diagnostic workflows, leading to a situation in which extensive detection of variants is only partially matched by the experimental efforts required to establish their biological and clinical relevance. Bridging this gap will require coordinated research initiatives that bring together clinical genetics and basic biology, with dedicated support for functional studies that parallel the expanding use of high-throughput sequencing in clinical practice.

Decoding variants of uncertain significance through the clinical phenotype

Beyond computational prediction and functional testing, interpretation of VUS fundamentally relies on a phenotype-driven genetic hypothesis that evolves over time. In SAIDs, the clinical phenotype is often incomplete at presentation and can progressively unfold, providing critical context for variant interpretation through longitudinal follow-up, segregation analysis, treatment response and exclusion of alternative diagnoses. This clinical reasoning is particularly important given that most currently available variant classification tools primarily assist in classifying missense variants and can therefore bias interpretation towards apparent candidates while obscuring the true pathogenic variant, especially in the absence of functional validation. The risk of misattributing pathogenicity to a VUS underscores the need to continually reassess genetic hypotheses rather than prematurely

'solving' a case. This challenge is further shaped by the diversity of next-generation sequencing strategies used in clinical practice, ranging from targeted gene panels derived from exome data to WES and WGS; each of these strategies is associated with markedly different numbers and types of VUS detected, as well as with distinct blind spots (notably non-coding, structural or mosaic variants)[161]. Although a subset of clinical exomes yields a clear molecular diagnosis, a substantial proportion remains non-decisive, raising the question of when VUS should be deprioritized and when they might instead point towards digenic or multigenic inheritance[162,163]. In this context, careful integration of VUS with the clinical phenotype could represent the most accessible route to uncovering combinatorial genetic mechanisms underlying complex autoinflammatory disease, reinforcing the central role of clinical genetics alongside computational and experimental approaches.

Translational implications

Decoding variants of uncertain significance for rational therapies

The importance of decoding VUS to establish a genetic diagnosis and enabling access to therapies that are targeted to disease pathophysiology is exemplified by the case of a young patient diagnosed with life-threatening NLRC4-related macrophage activation syndrome after identification of an *NLRC4* variant previously characterized as pathogenic[164]. On the basis of accumulated knowledge about this variant and its associated disease, and under an emergency compassionate-use investigational new drug authorization from the FDA, the patient was treated with recombinant IL-18 binding protein, which led to a rapid improvement of her health.

Molecular decoding of VUS can also guide treatment selection. For example, a subset of CAPS-associated NLRP3 variants are resistant to the direct NLRP3 inhibitor MCC950 (also known as CRID3)[29,30,165], indicating that screening patients' variants for MCC950 resistance could help to stratify patients with CAPS and refine treatment decisions in the future.

Finally, decoding VUS can accelerate therapeutic innovation. A de novo variant in *IL1R1* (encoding IL-1 receptor type 1 (IL-1R1)) was identified in a patient with chronic non-bacterial osteomyelitis[166]. Functional studies revealed that this p.K131E variant abolished the binding of the IL-1 receptor antagonist (IL-1Ra) to IL-1R1 while preserving binding of IL-1α and IL-1β. Consequently, peripheral blood mononuclear cells from this patient were refractory to IL-1Ra antagonism but remained responsive to IL-1 cytokines. On the basis of these results, the patient was treated with canakinumab (an IL-1β-neutralizing antibody), resulting in rapid clinical improvement. Importantly, this mechanistic insight also led to the design of an improved IL-1 trap protein: a decoy IL-1 receptor carrying the p.K131E mutation that retains IL-1β and IL-1α binding while lacking IL-1Ra binding, thereby maintaining the neutralization of pro-inflammatory IL-1 without affecting the anti-inflammatory actions of IL-1Ra[166].

From prediction of variants of uncertain significance to clinical classification

Using specific SAID examples, we have shown that genetic information, in silico predictions and functional assays each have intrinsic limitations and that translating a characterization of a variant as hypomorphic or hypermorphic into a classification of pathogenic or benign is not straightforward. To address this problem, international guidelines and recommendations — most notably those of the American College of Medical Genetics and Genomics — have been developed to integrate clinical phenotype, segregation analysis data, allele frequency, in silico predictions and functional evidence into a standardized classification framework (Box 1).

Crucially, the strength of several criteria used for variant classification depends on the number of independent observations (for example, the recurrence of the same variant in unrelated families), highlighting the importance of sharing both clinical and biological data. Publicly available databases such as ClinVar and Infevers provide essential platforms for submitting variants together with associated clinical information[21,167].

Thus, a roadmap towards more accurate variant classification, and ultimately towards rendering the designation VUS obsolete[168], is emerging (Supplementary Fig. 2). DMS should be performed on SAID-associated genes owing to their own specificities — notably the arms race with pathogens — with priority given to those displaying GoF effects[29,93]. In parallel, in silico tools tailored to address the challenges of GoF and IDR-containing proteins must be developed. Combined with systematic collection and sharing of genetic and clinical data from people with SAIDs, these efforts will generate large, high-quality datasets that enable benchmarking, refined machine learning and improvement of AI-based prediction. For rheumatologists and geneticists, this evolving synergy promises to transform the interpretation of variants in the context of SAIDs. We believe that accurate annotation of all possible missense variants in genes implicated in monogenic SAIDs is an achievable goal that will ultimately support earlier and more precise diagnosis and treatment.

Conclusions

The past 10 years have witnessed a large increase in publicly available genomic data, major advances in 3D protein structure prediction, the development of machine learning and AI and the advent of large-scale mutagenesis screens[29,93–95,169]. Together, these developments have substantially improved the classification of LoF variants in the context of monogenic SAIDs. Nevertheless, important gaps remain, particularly in the in silico prediction of IDR-containing proteins. Moreover, many databases are outdated and have not incorporated these recent advances. At present, the functional effects of GoF variants remain especially difficult to predict owing to the limited accuracy of existing computational tools. The next frontier will be to unravel the contribution of missense VUS to complex SAIDs (Box 4). Insights from monogenic SAIDs will provide a foundation, but new methods will be required to measure the combinatorial effects of multiple low-penetrance variants with minor hypomorphic or hypermorphic effects. Large genomic, biologic and clinical data such as those gathered by the UK biobank[34,170] should contribute to such an effort. Finally, missense variants represent only the tip of the iceberg as coding sequences account for less than 2% of the human genome, and the contribution of non-coding variants to SAIDs remains a largely unexplored field.

Published online: 26 May 2026

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Acknowledgements
S.S. is funded by Kennedy Trust Senior Fellowship and MRC project grant number MR/Y011945/1.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41584-026-01380-8.

Peer review information *Nature Reviews Rheumatology* thanks Adriana de Jesus, Marco Gattorno and Isabelle Meyts for their contribution to the peer review of this work.

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https://doi.org/10.1038/s41584-026-01386-2

Review article

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The evolving comorbidity landscape of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is associated with a wide spectrum of comorbidities that substantially influence quality of life and long-term outcomes. These include extra-articular manifestations, cardiovascular disease, cerebrovascular accidents, dementia, malignancy, infection, mental health disorders and osteoporosis. Patterns of comorbidity in RA have evolved over the past three decades, with declining prevalence of some complications alongside persistently high or increasing burdens of interstitial lung disease, anxiety and depression. Shifts in the comorbidity landscape probably reflect advances in RA management, including the expanded use of biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) and a widespread adoption of treat-to-target strategies. Consideration of comorbidity-specific epidemiology, the potential effect of DMARDs on comorbidity risk and opportunities to address both RA and comorbid disease are increasingly relevant in clinical care. Preventive strategies, including selected enhanced screening approaches such as those for cervical cancer, interstitial lung disease, cardiovascular disease and osteoporosis, form an important component of comprehensive RA management. Awareness of the changing comorbidity landscape could support more integrated and individualized care for people with RA.

Sections

Introduction

Extra-articular manifestations

Vascular diseases and dementia

Malignancy

Infection

Mental health

Osteoporosis

Conclusions

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Key points

- Incidence of non-severe extra-articular manifestations, cardiovascular disease and overall malignancy in rheumatoid arthritis (RA) is decreasing, whereas interstitial lung disease, anxiety and depression remain prevalent, despite therapeutic advances.
- Disease-modifying antirheumatic drug (DMARD) selection in RA should incorporate patient-specific comorbidities to enable more individualized, risk-aware disease management.
- Preventive screening in RA generally follows population guidelines, with important exceptions including enhanced cervical cancer screening in individuals receiving DMARDs and earlier, more frequent osteoporosis screening in individuals treated with glucocorticoids.
- Increased clinical awareness is needed to enable timely screening for interstitial lung disease, cardiovascular disease, cervical cancer and osteoporosis in individuals with RA.
- Control of RA-related inflammation through a treat-to-target strategy is imperative to reduce the risk of comorbidities in RA.
- Comparative effectiveness studies and randomized controlled trials are needed to clarify the associations between DMARDs and RA-related comorbidities.

Introduction

Rheumatoid arthritis (RA) affects an estimated 0.5–1.0% of the global population, with both incidence and prevalence continuing to rise worldwide[1–4]. Despite major therapeutic advances in the late twentieth century — most notably the introduction of biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) — and the widespread adoption of treat-to-target strategies in the early twenty-first century, people with RA continue to have excess morbidity and mortality compared with the general population. This excess risk is driven largely by cardiovascular disease (CVD), malignancy and respiratory disease, and more than half of patients have at least one comorbidity at the time of RA diagnosis[4–8] (Fig. 1).

Comorbid disease has important implications for prognosis in RA. Outcomes are poorest among older individuals with multiple comorbidities, whereas those with fewer comorbidities are more likely to achieve remission and have mortality rates comparable to the general population[9,10]. Studies of multimorbidity (that is, the coexistence of two or more chronic conditions) published in 2014–2022 have shown that people with RA have a two-fold higher prevalence of multimorbidity compared with individuals without RA and accrue chronic conditions at a faster rate[11–14]. Specific multimorbidity clusters, including those involving mental health and substance-use disorder, chronic pain and CVD, are associated with higher disease activity and worse functional status[15]. Notably, an increased risk of several comorbidities is evident both prior to, and following, RA diagnosis, showcasing the potential bidirectional relationship between RA and comorbid disease[16,17].

Mechanistic insights increasingly support this bidirectional relationship. Certain comorbidities seem to predispose individuals to the development of RA (for example, respiratory disease as part of the mucosal origins hypothesis), whereas the systemic inflammation characteristic of RA accelerates the onset and progression of additional comorbidities (such as CVD). Epidemiologic studies in the pre-RA phase (defined by systemic autoimmunity in the absence of clinically apparent RA), further support this bidirectional relationship and show an increased incidence of certain comorbidities (such as CVD, lung disease, endocrine disorders and mental health conditions)[16,18]. Together, these observations underscore the need for comprehensive, longitudinal management strategies that address both RA and co-existing medical conditions.

In this Review, we examine how the comorbidity landscape in RA has evolved alongside changes in population health, expanding use of biologic and targeted synthetic DMARDs and widespread adoption of treat-to-target approaches in clinical practice. We focus on major comorbidities encountered in RA, including extra-articular manifestations, cardiovascular and cerebrovascular disease, dementia, malignancy, infection, mental health disorders and osteoporosis. For each comorbidity, we consider changes in epidemiology, implications for RA treatment selection and opportunities to integrate prevention and screening into routine care (Fig. 2). Through this approach, we aim to support clinicians in providing a more personalized approach to the management of RA.

Extra-articular manifestations

Extra-articular manifestations are systemic inflammatory complications of RA that occur outside the synovial joints and arise directly from underlying disease mechanisms. These manifestations reflect immune-mediated involvement of multiple organs and tissues — most often the skin (for example, rheumatoid nodules), the lungs (such as interstitial lung disease, ILD), the eyes (including scleritis), vasculature (such as rheumatoid vasculitis) and the haematologic system (for example, Felty syndrome). Recognition and management of these manifestations require an integrated approach that extends beyond control of joint inflammation.

Epidemiology

Extra-articular manifestations occur in approximately 20–40% of individuals with RA, and are more frequently observed in association with high disease activity, male sex, history of smoking, increased pro-inflammatory markers and high rheumatoid factor titres[19–21]. Epidemiological data suggest that the prevalence of these manifestations has declined over time. A population-based inception cohort from Olmsted County, Minnesota, USA showed a substantial reduction in the 10-year cumulative incidence of extra-articular manifestations, from 45% among people diagnosed between 1985 to 1999 to 32% among those diagnosed between 2000 and 2014, paralleling improvements in RA management. Notably, declines were most pronounced for keratoconjunctivitis sicca (dry eye syndrome) and subcutaneous nodules, whereas Sjogren disease, bronchiolitis obliterans and cervical myelopathy showed nonsignificant downward trends. Given that even non-severe extra-articular manifestations confer an increase of more than 80% in mortality risk compared with RA without extra-articular manifestations, these epidemiological shifts could have important implications for long-term survival in the RA population[19].

The epidemiology of severe extra-articular manifestations (including neuropathy, serositis, vasculitis, episcleritis, retinal vasculitis and glomerulonephritis) has shifted substantially, with marked declines observed in conditions such as rheumatoid vasculitis since 2000 (ref. 19). Emerging evidence suggests that this trend reflects a combination of broader population-level changes — most notably reduced smoking prevalence — and the transformative impact of modern DMARDs and

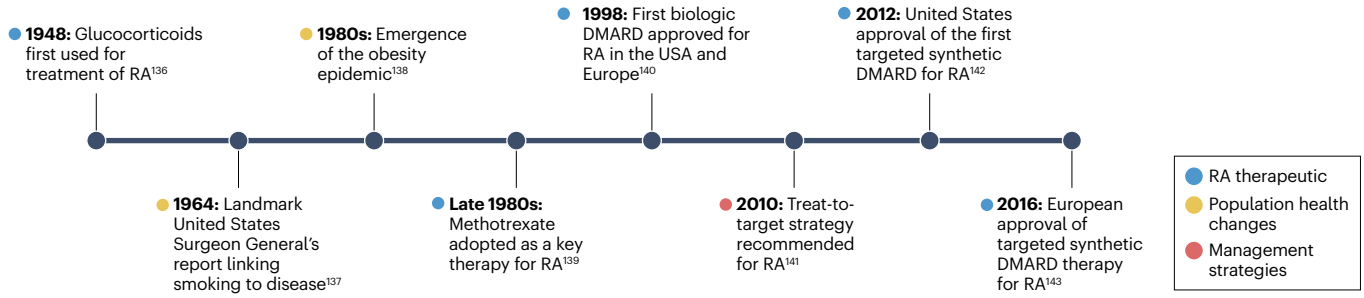

Fig. 1 | Timeline of advances in rheumatoid arthritis disease management and population-level health changes. Advances in rheumatoid arthritis (RA) management have occurred alongside major population-level health changes, together shaping the evolving comorbidity landscape in RA[136–143]. DMARD, disease-modifying antirheumatic drug.

treatment strategies[19]. Felty syndrome, once a well recognized clinical entity, has become increasingly uncommon in contemporary RA cohorts; in a 2024 study of 270 people with RA, only a single individual exhibited the classic Felty syndrome triad of RA, autoantibody positivity, neutropenia and splenomegaly, with neutropenia in the remaining cases largely attributed to RA therapies, including methotrexate and the interleukin IL-6 inhibitors[22]. This downward trajectory in severe extra-articular manifestations of RA carries important prognostic implications, given that these manifestations confer more than a three-fold increase in mortality risk, and declining incidence could therefore contribute to improved long-term outcomes among people with RA[19].

Clinically meaningful ILD occurs in approximately 5–15% of individuals with RA, and carries a poor prognosis, with median survival ranging from 2 to 14 years and a more than two-fold increase in mortality compared with individuals with RA without ILD[19,23,24]. In a retrospective population-based cohort from Minnesota, the 20-year cumulative incidence of ILD decreased from 6.3% among people with RA diagnosed between 1955 and 1994 to 4.2% among those diagnosed between 1999 and 2014; however, this reduction did not reach statistical significance[23]. Such epidemiological data thus indicates that the incidence of RA-associated ILD has plateaued[23], in contrast to the substantial declines observed for other extra-articular manifestations. This divergence highlights the complex interplay of modifiable and non-modifiable risk factors that continue to sustain the burden of RA-associated ILD. Important non-modifiable risk factors — including older age at RA onset, male sex, and seropositivity — remain immutable contributors to ILD risk, potentially limiting the impact of therapeutic advance on RA-associated ILD[23,25]. At the same time, greater clinical awareness and expanding use of chest high-resolution computed tomography (HRCT) could be increasing the detection of subclinical ILD, thereby partially masking true reductions in incidence over time. As a result, distinguishing epidemiological trends from surveillance effects has become a challenge in interpreting the incidence of RA-associated ILD. Further studies will be essential to disentangle these dynamics and to clarify whether the stable incidence reflects persistent pathogenic drivers not targeted by current therapies, evolving screening practices or both. Improved risk-stratification tools to identify individuals at highest risk for the development and progression of RA-associated ILD will be critical for guiding targeted screening strategies.

Pharmacological management

Among the extra-articular manifestations of RA, the distinct therapeutic implications for ILD warrant separate consideration because of its substantial contribution to morbidity and mortality. Increasing observational evidence suggests that several DMARDs are safer than previously recognized in individuals at risk for RA-associated ILD and some DMARDs might even attenuate progression of RA-associated ILD. In a multinational prospective cohort, methotrexate use was not associated with an increased risk of ILD compared with non-use among people with RA, challenging earlier concerns regarding pulmonary toxicity[26]. Furthermore, in a multicentre, retrospective cohort study, treatment with mycophenolate, azathioprine or rituximab was associated with an improved pulmonary function test trend over 12 months in individuals with RA-associated ILD compared with those who did not initiate treatment[27]. In a retrospective propensity score-matched cohort study of United States veterans with RA-associated ILD, initiation of tumour necrosis factor (TNF) inhibitors resulted in similar risks of respiratory hospitalization, all-cause mortality and respiratory mortality compared with non-TNF inhibitor biologic or targeted synthesis DMARDs[28]. Despite these encouraging findings, the evidence remains limited by confounding and selection bias inherent to observational study designs, underscoring the need for randomized controlled trials to delineate causal effects of specific DMARDs. Advances in anti-fibrotic therapy, including nintedanib, pirfenidone and nerandomilast, have shown promise in stabilizing lung function in RA-associated ILD, as demonstrated in the INBUILD, TRAIL-1 and FIBRONEER studies, respectively, suggesting the potential for modifying long-term outcomes as these agents become more widely integrated into clinical practice[29–31].

Preventive care

Preventive care in RA-associated ILD focuses on early identification of individuals at the highest risk for disease development and progression, with the aim of enabling timely intervention and limiting irreversible lung damage. Screening approaches for RA-associated ILD are evolving as efforts intensify to identify at-risk individuals earlier in the disease course. The 2023 joint guidelines from the American College of Rheumatology (ACR) and the American College of Chest Physicians (CHEST) recommend consideration of HRCT and pulmonary function tests at the time of RA diagnosis in people with established risk factors for ILD, with annual reassessment using pulmonary function tests for those at persistently elevated risk[32]. These recommendations align with guidance from the European Respiratory Society (ERS) and European Alliance of Associations for Rheumatology (EULAR), who similary advocate targeted screening with chest HRCT in high-risk individuals[33] (Table 1). Collectively, these guidelines reflect a growing consensus that earlier detection — guided by clinical,

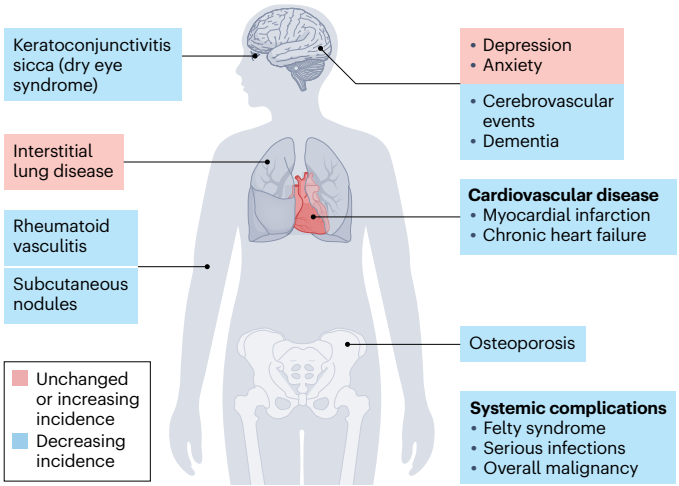

Fig. 2 | Changes in comorbidity incidence in rheumatoid arthritis. The comorbidity landscape in rheumatoid arthritis demonstrates heterogeneous temporal trends, with some conditions declining in frequency and others remaining stable or increasing over time. Selected major comorbidities with sufficient epidemiological data to assess temporal trends are shown. The time periods compared are not uniform across conditions and reflect the intervals reported in the underlying studies, usually spanning the early 2000s to the 2010s, with the majority of observed changes reported since approximately 2010. Trends depicted in the figure correspond to epidemiological studies cited in the relevant sections of the main text.

serologic and demographic predictors — might enable more timely intervention and improved characterization of disease trajectories in RA-associated ILD.

Efforts to refine risk stratification for RA-associated ILD highlight the growing recognition that early identification of high-risk individuals is essential for improving outcomes. In one case–control study, six fine-specificity autoantibodies associated with RA-associated ILD were identified and incorporated — together with smoking history, RA disease activity, glucocorticoid exposure and obesity — into a risk score that demonstrated high specificity for predicting ILD among people with RA[34]. Complementing these efforts, the ongoing multinational ANCHOR-RA study aims to develop a multivariable prediction model integrating serologic, clinical and demographic factors to better identify those most likely to benefit from targeted screening with chest HRCT[35]. In the prospective SAIL-RA cohort, the number needed to screen to detect one case of RA-associated ILD ranged from 3.6 to 6.4, depending on the screening strategy[35,36]. Additional work indicates that genetic risk scores might be helpful in individualized risk startification and screening for RA-associated ILD[37,38]. Because these tools undergo validation in external cohorts, they hold promise for enabling more personalized counselling, earlier detection, and improved mortality and morbidity through earlier treatment of RA-associated ILD.

Vascular diseases and dementia

RA is also associated with substantial cardiovascular and cerebrovascular morbidity. Vascular disease is therefore an important systemic complication of RA, and dementia is considered within this domain given its close relationship with vascular risk factors and underlying brain injury.

Epidemiology

Patients with RA have an increased risk of CVD and CVD-related mortality compared with the general population, with the leading causes of death being coronary artery disease and heart failure[7,39]. This excess risk reflects the combined effects of chronic systemic inflammation and traditional cardiovascular risk factors, including hypertension, dyslipidaemia, diabetes mellitus and cigarette smoking[1]. However, contemporary population-based cohorts from Norway and Minnesota show substantial improvements in cardiovascular outcomes among people with RA compared with historical data. Individuals diagnosed with RA in the past 15 years have rates of CVD events and CVD-related mortality comparable to those of individuals without RA[40–42]. These trends are corroborated by data from the US Veterans Health Administration, which demonstrate a progressive narrowing of excess CVD-related mortality in RA between 2000 and 2017, from 23% to 10%[7]. Together, these findings suggest that advances in DMARDs, earlier RA diagnosis and tighter control of RA have all meaningfully attenuated the cardiovascular burden associated with RA.

People with RA have a substantially increased burden of cerebrovascular disease. A population-based cohort study from Germany reported an elevated risk of stroke and transient ischaemic attack compared with the general population, with the excess risk most pronounced among individuals aged 18–40 years[43]. The excess risk probably reflects accelerated atherosclerosis, supported by case–control data demonstrating greater carotid plaque burden in people with RA than in the general population[44]. Epidemiologic trends suggest some improvement over time. A retrospective cohort study from Canada reported a decline in the risk of ischaemic stroke among individuals diagnosed with RA after 1999 compared with the general population[45], a finding further supported by data from Norway showing reduced stroke-related hospitalizations among people with RA between 1972 and 2013 (ref. 46). However, residual risk persists: men with RA continued to have an excess risk of stroke compared with the general population between 2007 and 2013. Although contemporary cohorts suggest a decline in cerebrovascular disease — probably reflecting improved RA disease control and better management of traditional cardiovascular risk factors — these observations underscore the need for vigilant risk assessment and integrated cardiovascular prevention strategies across the RA disease course.

Beyond overt cardiovascular and cerebrovascular events, vascular and inflammatory mechanisms in RA also contribute to an increased risk of cognitive decline and dementia. Evidence indicates that RA confers an elevated risk of dementia, with a 2023 meta-analysis reporting a nearly two-fold increase compared with the general population, implicating chronic inflammation as a potential driver[47]. Pro-inflammatory mediators involved in RA pathogenesis — such as TNF, IL-1, and IL-6 — are also elevated in Alzheimer disease, supporting shared mechanisms involving cerebral microvascular injury and microglial activations[48]. Despite the elevated risk of dementia, a retrospective study from Minnesota revealed declining rates of dementia among people with RA, with no excess risk relative to the general population by the 2000s[49]. These trends parallel improvements in cardiovascular and cerebrovascular outcomes in RA, suggesting that the use of biologic and targeted synthetic DMARDs and the adoption of treat-to-target strategies have had broader benefits for RA disease management.

Pharmacological management

Pharmacological strategies for cardiovascular risk mitigation in RA increasingly reflect a more nuanced understanding of how

Table 1 | Screening recommendations for common comorbidities in rheumatoid arthritis

Guideline or issuing body	Summary of recommendations	Ref.
Extra-articular manifestation: interstitial lung disease		
ATS clinical statement	Baseline chest computed tomography scan to screen for interstitial lung abnormalities and ILD	132
ACR–CHEST guideline	Screen individuals at increased risk of ILD[a] at RA diagnosis using pulmonary function tests and HRCT Consider annual rescreening with pulmonary function tests	32
ERS–EULAR clinical practice guidelines	Screen individuals with risk factors for ILD (older age, smoking history, elevated rheumatoid factor or anti-CCP antibodies, increased inflammatory markers, male sex or high disease activity) Recommend HRCT as the preferred screening modality	33
Cardiovascular disease, cerebrovascular disease and dementia		
EULAR initiative	Documentation of history of myocardial infarction, angina, coronary revascularization, stroke, transient ischaemic attack, heart failure and lower limb peripheral arterial disease Document cardiovascular risk factors including smoking status, BMI, hypertension, hypercholesterolaemia, renal insufficiency and estimated cardiovascular risk using SCORE-based models Document current cardiovascular treatments	133
EULAR recommendation	Optimize RA disease activity control Assessment cardiovascular risk at least once every 5 years in accordance with national guidelines or using SCORE-based cardiovascular risk prediction model, incorporating total cholesterol and high-density lipoprotein cholesterol Apply a 1.5 multiplier to cardiovascular risk prediction models Measure lipids when disease activity is stable or in remission Consider carotid ultrasonography to assess asymptomatic plaque Promote healthy diet, regular exercise and smoking cessation Use antihypertensives and statins as indicated Use NSAIDs cautiously and minimize glucocorticoid exposure	64
International Expert Panel	Communicate increased cardiovascular risk in RA to the patient's primary care provider every 2 years Perform cardiovascular risk assessment, lipid profiling and haemoglobin A1c testing, in accordance with national guidelines, within the first 2 years after RA diagnosis Initiate management of cardiovascular risk factors in individuals at intermediate or high risk Document smoking status, tobacco use and BMI annually Measure blood pressure at ≥80% of clinic visits and initiate treatment if ≥140/80 mmHg	134
Malignancy		
Expert opinion	Women receiving immunosuppressive therapy should undergo cervical cancer screening in accordance with recommendations used for women with HIV	81
EULAR initiative	Document history of malignancy Document completion of age-appropriate cancer screenings for malignancy (mammography, cervical screening, skin examamination and colonoscopy) Document risk factors for malignancy, including family history and inflammatory bowel disease	133
Infection		
ACR guideline for vaccinations	Consider high-dose or adjuvanted influenza vaccination based on patient age and immunosuppression Recommend recombinant zoster and pneumococcal vaccination in individuals receiving immunosuppression Consider HPV vaccination in individuals aged 26–45 years receiving immunosuppression Consider withholding methotrexate for 2 weeks after to influenza vaccination Administer non-live attenutated vaccines in individuals receiving ≤10 mg prednisone daily equivalent	98
EULAR recommendation	Assess vaccination status and need for further vaccination annually Coordinate vaccination planning among the rheumatologist, patient and primary care provider Preference for administration of vacination during disease quiescent and prior to immunosuppression initiation when feasible Consider non-live vaccines in individuals receiving glucocorticoids and/or DMARDs Use live-attenuated vaccines cautiously in selected individuals receiving immunosuppression Strongly consider influenza and pneumococcal vaccination for people with RA	135
Mental health		
EULAR initiative	Document previous or current depression Document completion of screening for depression Document current treatment for depression	133

Table 1 (continued) | Screening recommendations for common comorbidities in rheumatoid arthritis

Guideline or issuing body	Summary of recommendations	Ref.
Osteoporosis		
EULAR initiative	Document previous osteoporotic fracture Assess risk factors including low BMI (<19), physical inactivity, glucocorticoid use, alcohol use, family history of femoral neck fracture, and secondary osteoporosis Measure bone mineral density when applicable Calculate FRAX global fracture risk when applicable Document current or previous treatment for osteoporosis	133
ACR guideline	For individuals aged ≥40 years receiving ≥2.5 mg glucocorticoids daily for >3 months, assess fracture risk using FRAX and bone mineral density by DXA with vertebral fracture assessment or spinal radiography For individuals aged <40 years and receiving ≥2.5 mg glucocorticoids daily for >3 months, assess bone mineral density by DXA with vertebral fracture assessment or spinal radiography Provide counselling on adequate calcium and vitamin D intake in individuals receiving glucocorticoids	125

[a]High-titre rheumatoid factor or titre anti-cyclic citrullinated peptide (CCP) antibodies, smoking, older age at rheumatoid arthritis (RA) onset, high disease activity, male sex and higher body mass index (BMI). ACR, American College of Rheumatology; ATS, American Thoracic Society; CHEST, American College of Chest Physicians; DMARD, disease-modifying antirheumatic drug; DXA, dual-energy X-ray absorptiometry; ERS, European Respiratory Society; EULAR, European Alliance of Associations for Rheumatology; FRAX, fracture risk assessment tool; HRCT, high-resolution computed tomography; HIV, human immunodeficiency virus; HPV, human papilloma virus; ILD, interstitial lung disease; NSAID, non-steroidal anti-inflammatory drug; SCORE, Systematic Coronary Risk Evaluation.

immunomodulatory therapies interact with cardiometabolic pathways. Methotrexate has long been hypothesized to exert cardioprotective effects through suppression of systemic inflammation[50]. However, the Cardiovascular Inflammation Reduction Trial (CIRT) found no benefit of methotrexate for secondary cardiovascular prevention in non-RA populations with previous myocardial infarction or multivessel coronary artery disease and either type 2 diabetes mellitus or metabolic syndrome[51]. These findings suggest that any cardiovascular benefit of methotrexate might be restricted to conditions characterized by active systemic inflammation. However, the null result in CIRT might also reflect trial design considerations, including the inclusion of participants without elevated inflammatory markers and the use of relatively low doses of methotrexate. Consistent with this interpretation, observational data in RA indicate that methotrexate use is associated with a reduction in cardiovascular events of more than 20%, independent of changes in RA disease activity, suggesting that cardiovascular risk reduction could occur through mechanisms beyond direct control of RA inflammation[52].

Biologic DMARDs exhibit heterogeneous cardiovascular profiles. Despite increases in lipid levels, the IL-6 receptor inhibitor tocilizumab did not increase rates of major adverse cardiovascular events compared with the TNF inhibitor etanercept in the ENTRACE trial, which included people with seropositive RA, prior failure of conventional synthetic DMARDs and at least one cardiovascular risk factor, underscoring the complex interplay between inflammation, lipid metabolism and cardiovascular risk in RA[53]. By contrast, the Oral Rheumatoid Arthritis Trial Surveillance (ORALSURV) study reported an increased risk of major adverse cardiovascular events with tofacitinib compared with TNF inhibitors[54]. This risk seems to be modifiable through careful patient selection: limiting tofacitinib use to individuals without a history of atherosclerotic CVD, and considering concomitant statin therapy when treatment is warranted in those with a history of atherosclerotic CVD or high cardiovascular risk, might mitigate cardiovascular risk[54–56]. Evidence from comparative treatment trials further supports the importance of inflammation control. In the TARGET trial, people with active RA receiving methotrexate were randomly allocated to receive either a TNF inhibitor or escalation to combination therapy with sulfasalazine and hydroxychloroquine; both strategies led to reductions in vascular inflammation, supporting the concept that uncontrolled RA disease activity, rather than specific treatment selection, is the key driver of cardiovascular risk[57].

The Trial of Atorvastatin in Rheumatoid Arthritis (TARA) randomized controlled trial found that statin therapy mediated modest anti-inflammatory effects, with reductions in disease activity score with 28 joints (DAS28) and inflammatory markers at 6 months compared with placebo in people with RA, demonstrating benefits for both hyperlipidaemia management and inflammation[58]. Collectively, these findings highlight the importance of individualized treatment selection that considers both the RA disease activity and comorbid cardiovascular risk, while underscoring the unmet need for robust risk-stratification tools and targeted cardioprotective strategies in RA.

Preventive care

Preventive cardiovascular care in RA focuses on aggressive modification of traditional risk factors alongside optimal control of systemic inflammation. Smoking cessation remains a central priority, given that smoking influences RA disease development and progression, and is associated with higher disease activity and reduced quality of life[59–61]. Smoking cessation is particularly important for the prevention of CVD-related events: a 2020 study reported a 30% reduction in cardiovascular events among former smokers with RA compared with current smokers, alongside improvements in hyperlipidaemia and hypertension[59]. Evidence also supports the effectiveness of structured cessation interventions. In a randomized controlled trial, people with RA enrolled in a 6-week intensive smoking cessation programme were four times more likely to achieve smoking cessation at 3 months than those receiving standard care[62]. When counselling people on smoking cessation, clinicians should emphasize that improvements in RA disease activity following smoking cessation can take time, reflecting the gradual recovery of immune function. Accordingly, smoking cessation should be prioritized as a core element of RA care, with sustained support to maintain abstinence given that cardiovascular and disease-related benefits accrue over time.

Assessment of lipid profiles in RA is complicated by the suppressive effects of systemic inflammation on low-density lipoprotein cholesterol, which can obscure the underlying atherosclerotic risk[63]. Consequently, standard CVD risk calculators often underestimate the risk of CVD-related events in RA, because systemic

inflammation is not incorporated into most prediction models. However, neither RA-specific risk calculators nor application of the EULAR-recommended 1.5 multiplier to traditional CVD risk scores has improved risk prediction compared with standard calculators[61,64,65]. Alternative strategies to better assess CVD risk in people with RA include carotid ultrasonography and measurement of high-sensitivity cardiac troponin T[61,63]. For cardiovascular risk management, the 2018 American College of Cardiology/American Heart Association guideline on the management of blood cholesterol recommends statin therapy for individuals aged 40–75 years with RA who have an intermediate 10-year risk of a cardiovascular event[66]. Regarding aspirin, a subgroup analysis of people with RA receiving chronic non-steroidal anti-inflammatory drugs (NSAIDs) in the PRECISION trial found similar risks of major adverse cardiovascular events and NSAID-related toxicity among those using low-dose aspirin for primary CVD prevention and those not using aspirin, suggesting that cardiovascular risk mechanisms in RA might differ from those in the general population and might be driven by the chronic inflammatory state[67]. Collectively, these findings highlight the need for improved cardiovascular risk-prediction models tailored to RA and for prevention strategies that more effectively address the residual cardiovascular burden.

Malignancy

People with RA have an estimated 20% increased risk of cancer compared with the general population — an elevation thought to reflect the cumulative effects of chronic systemic inflammation[7,68,69]. Although improved RA disease control using DMARDs has the potential to mitigate cancer risk, individual therapies introduce immunosuppressive effects that can impair immunosurveillance, requiring a careful therapeutic balance[68].

Epidemiology

Population-based studies report encouraging downwards trends in certain malignancy-related outcomes in both the USA and France. In a large study of United States veterans, the risk of cancer-related mortality in RA declined from 27% in the 2000s to 9% in the 2010s, with a 21% reduction in incident lymphoma risk[7,68]. Similarly, in France, DMARD exposure during the 2010s was associated with a statistically significant reduction in the risk of non-Hodgkin lymphoma[70]. However, trends have not been uniform: registry data from Sweden indicate comparable lymphoma risks in contemporary and historical RA cohorts[71].

Emerging evidence also challenges the prior assumption that lung cancer risk in RA is primarily driven by the shared risk factor of smoking. In a 2024 study of more than 70,000 United States veterans, RA was associated with an over 50% increased risk of lung cancer independent of smoking status[72]. These findings suggest that factors beyond smoking, such as chronic systemic inflammation or extra-articular manifestations including RA-associated ILD, might contribute to lung cancer risk in RA.

Pharmacological management

Pharmacological management of RA requires careful consideration of malignancy risk, given that both the disease itself and immunomodulatory therapies can influence cancer susceptibility. A 2022 systematic review and meta-analysis reported that people with RA treated with conventional synthetic DMARDs had an approximately 15% increased overall risk of malignancy compared with the general population, whereas biologic DMARDs did not seem to confer additional risk[73]. Notably, no association was observed between tumour mutational burden and incident cancer, suggesting that elevated cancer risk in RA is driven predominantly by chronic systemic inflammation rather than by DMARD exposure[73]. Observational data further indicate heterogeneous malignancy risk profiles across DMARDs. In a meta-analysis, rituximab, tocilizumab and tofacitinib were not associated with an increased risk of malignancy relative to conventional synthetic DMARDs or TNF inhibitors[74]. By contrast, abatacept was associated with a modestly increased risk of overall malignancy and non-melanoma skin cancer, a finding also observed in a large Swedish observational cohort[74,75]. In addition, the ORALSURV randomized controlled trial reported a 48% higher risk of incident cancer among people with RA assigned to receive tofacitinib compared with those assigned to receive TNF inhibitors[54].

Overall, the current evidence highlights the intertwined contributions of RA-related inflammation and therapeutic immunosuppression to malignancy risk. These findings highlight the need for caution when considering Janus kinase (JAK) inhibitors in individuals with a prior history of malignancy and when considering abatacept in individuals with a prior history of melanoma. Ongoing vigilance among primary care providers and rheumatologists remains important to facilitate timely cancer evaluation in this high-risk population. Further well designed observational studies are needed to better delineate malignancy risk across individual DMARDs.

Preventive care

Preventive cancer screening in RA generally follows population-based guidelines for breast, colorectal, lung and prostate cancer screening[76–80]. Important exceptions reflect the heightened vulnerability associated with chronic inflammation and immunosuppressive therapy. In women with RA receiving immunosuppression, intensified cervical cancer screening is recommended, with application of screening protocols developed for women with human immunodeficiency virus (HIV) because of the increased risk of persistent human papilloma virus (HPV) infection and cervical dysplasia[81] (Table 1). Despite these recommendations, observational data suggest that cervical cancer screening among women with RA is frequently delayed relative to recommended screening intervals, undermining preventive care and calling for closer collaboration between primary care providers and rheumatologists[82].

For lung cancer, current United States Preventive Services Task Force guidelines recommend that clinicians apply general population screening criteria to individuals with RA, including annual low-dose chest computed tomography for adults aged 50–80 years with a smoking history of ≥20 pack-years who currently smoke or who quit smoking within the past 15 years[80]. However, given emerging evidence that lung cancer risk in RA is increased independent of smoking status, these recommendations might evolve in the future[72]. Initial studies of lung cancer screening outcomes have reported similar screening detection rates for lung cancer in individuals with RA and the general population, although with a higher frequency of incidental parenchymal findings in RA[83]. In addition, given the increased risk of skin cancer in RA and with certain DMARDs (including methotrexate, TNF inhibitors, abatacept and JAK inhibitors), a low threshold for annual skin examination and timely dermatological referral is warranted[84]. Together, these considerations highlight the need for multidisciplinary vigilance in the development and implementation of cancer-screening strategies for the RA population to mitigate malignancy burden.

Infection

Although infections are not classically thought of as a co-morbidity in RA, given the typically acute rather than chronic nature of infectious

conditions, evolving epidemiological trends in RA warrant inclusion of infections in this Review. Patients with RA are at increased risk of infection owing to both disease-related immune dysregulation and the immunosuppressive effects of DMARDs. Older age, smoking history, comorbidities, seropositivity and high disease activity — as reflected by elevated DAS28 score — are all associated with increased risk of infection-related hospitalization and mortality[85,86]. In the following section, we discuss the changing epidemiology of infections in RA, ways to decrease infection risk when prescribing immunosuppressive medications, and the role of collaboration between the primary care provider and rheumatologist in prevention of infections.

Epidemiology

Evidence from population-based cohorts highlights the elevated risk of infection in people with RA. In two cohort studies from Denmark, people with RA were at an elevated risk of *Staphylococcus aureus* bacteraemia compared with the general population, as well as an elevated risk of osteoarticular infection relative to individuals without RA, with further risk amplification associated with TNF inhibitor use[87,88]. However, temporal trends suggest improvement over time. In a population-based inception cohort that included people with RA, rates of serious infections declined between 1955 and 2007 (ref. 89). Consistent with this finding, a retrospective study from Japan reported fewer infection-related hospitalizations among people initiating biologic or targeted synthetic DMARDs after 2010, alongside with lower disease activity and reduced glucocorticoid exposure, compared with earlier treatment eras[90]. Collectively, emerging evidence suggests that improved disease control of RA reduces the overall risk of serious infections, despite the inherent immunosuppressive effects of many DMARDs. Nonetheless, infection risk varies across DMARDs, with certain DMARDs more strongly associated with infectious complications. Accordingly, clinicians should incorporate a patient's history of prior infections into therapeutic decision-making to optimize safety while achieving remission or low disease activity.

Pharmacological management

Pharmacological management of RA requires careful consideration of infection risk, given that immunomodulatory therapies differ substantially in risk of infection. Although conventional synthetic DMARDs are associated with an increased risk of serious infections, multiple studies have shown that biologic and targeted synthetic DMARDS are associated with higher rates of serious infections, including tuberculosis reactivation and opportunistic infections. In particular, clinicians should remain vigilant for hepatitis B virus reactivation with rituximab and for reactivation of latent tuberculosis with TNF inhibitors[91,92]. In a systematic literature review and meta-analysis of phase II and III randomized controlled trials of JAK inhibitors (tofacitinib, baricitinib and upadacitinib), increased incidence rates of herpes zoster were observed, consistent with prior observational data[93,94]. In a prospective cohort study from the CorEvitas registry, methotrexate and TNF inhibitors were associated with higher incidence rates of overall and opportunistic infections compared with other DMARDs, with TNF inhibitors conferring a >50% increase in incidence rate ratio[95]. Tocilizumab, an IL-6 inhibitor, has been associated with an increased risk of gastrointestinal perforation related to diverticulitis compared with other DMARDs (such as rituximab and abatacept) and in the NORD-STAR trial, the incidence of infections was highest among those treated with tocilizumab in combination with methotrexate compared with other treatment arms (that is, active conventional therapy, certolizumab plus methotrexate and abatacept plus methotrexate)[96,97]. By contrast, hydroxychloroquine and sulfasalazine are not generally considered immunosuppressive[98]. Glucocorticoid use remains of particular concern: even low doses (≤7.5 mg prednisolone daily equivalent) substantially increase the risk of *Staphylococcus aureus* bacteraemia, and higher doses are associated with a nine-fold increase in infection risk, with a clear dose-dependent association with hospitalization-requiring infections[99,100]. Together, the data presented underscore the importance of balancing disease control in RA with possible immunosuppressive-related infection risk when selecting pharmacological treatment for RA.

Preventive care

Preventive care in RA aims to minimize infection risk and subsequent hospitalization through vaccination and systematic screening for latent infections prior to initiating immunosuppressive therapy. An important reference for both primary care providers and rheumatologists is the 2022 ACR guideline for vaccinations in people with rheumatic and musculoskeletal diseases, which outlines the vaccines that should be prioritized in people treated with DMARDs and how DMARD dosing can be adjusted to maximize vaccine immunogenicity[98]. Vaccination against herpes zoster is recommended for all people with RA, especially for those treated with IL-6 inhibitors or JAK inhibitors[93]. Prior studies have shown that people with RA have suboptimal vaccination rates, and that a physician's recommendation is an independent predictor of vaccine uptake across all vaccine types[101,102]. Screening for chronic hepatitis B should be considered prior to initiation of immunosuppressive medications, as endorsed by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver[103,104]. Collaboration between primary care providers and rheumatologists is imperative to ensure timely vaccination in people with RA to reduce infection-related complications in this high-risk population, and to ensure appropriate screening for latent infections before initiation of immunosuppressive DMARD therapy (Table 1).

Mental health

Depression and anxiety are common and clinically important comorbidities in RA, that contribute to disease burden, quality of life and long-term outcomes. Depression affects 14–48% of people with RA, and is associated with an increased risk of seronegative RA. Indeed, observational studies support a bidirectional relationship between RA and depression[105,106]; although Mendelian randomization analyses have not confirmed a causal link[107]. Anxiety also occurs more frequently in RA, with seropositivity conferring a four-fold increased risk[108,109]. Despite an incomplete understanding of the mechanisms linking mental health disorders and RA, attention to mental health remains an important component of routine RA care[107].

Epidemiology

Although a meta-analysis published in 2020 reported notable improvements in disease activity and quality-of-life during the first 5 years following RA diagnosis when comparing cohorts before and after 2002, no corresponding improvements were observed in depression and anxiety (nor in pain, fatigue and functional disability)[110]. In parallel, the incidence of anxiety and concomitant anxiety and depression seem to be increasing among people with RA compared with those without RA[108]. The mechanisms underlying these trends remain incompletely understood. Proposed contributors include increased awareness of mental health conditions by people and providers, central pain

sensitization and the effects of pro-inflammatory cytokines on the hypothalamic–pituitary–adrenal axis, which might contribute to fatigue and mood disturbances[111].

Pharmacological management

Although the risk of depression and anxiety is increased in people with RA compared with the general population, evidence to guide the use of specific anti-depressants in this setting remains limited. Available studies suggest that agents such as duloxetine and sertraline (commonly used antidepressants) could confer benefit in people with RA[112]. However, randomized controlled trials are necessary to establish the efficacy of these drugs and to determine whether particular anti-depressants are better suited to people with RA based on disease characteristics or underlying pathophysiology[112]. Notably, non-pharmacological approaches, including psychological therapies, mindfulness-based interventions and physical rehabilitation, should be considered for people with RA and concomitant depression or anxiety to address the complex management of the disease[113].

Preventive care

Early identification of depression and anxiety is recommended in routine clinical care for all adults and is particularly relevant in RA. The United States Preventive Services Task Force recommends screening for anxiety and depression in all adults[114,115]. In this context, a comparative study found that a positive depression screen on the Multidimensional Health Assessment Questionnaire (MDHAQ), a routinely used patient-reported outcome measure in RA, showed good concordance with other validated depression screening instruments, including the Patient Health Questionnaire 9 (PHQ-9) and the Hospital Anxiety and Depression Scale depression domain (HADS-D), suggesting a possible role for MDHAQ in assessing both disease activity and depressive symptoms in people with RA[116].

Osteoporosis

Osteoporosis represents a clinically important complication of RA. Disease-related inflammation and reduced physical function contribute to bone loss while glucocorticoid therapy (which is frequently used to control RA disease activity) further amplifies fracture risk.

Epidemiology

Epidemiological data suggest that the burden of osteoporosis in RA has changed over time. A population-based study from Germany reported a statistically significant decline in the prevalence of osteoporosis among people with RA from 20% in 2007 to 6% in 2017 (ref. 117). This improvement coincided with reductions in disease activity and glucocorticoid use, as well as increased prescriptions of calcium and vitamin D independent of glucocorticoid exposure, which might have contributed to the observed trend[117]. Despite this decline in osteoporosis prevalence, a study from Japan reported an increased risk of fractures from 2011 to 2023, even alongside higher rates of RA remission, greater biologic DMARD use and increased prescriptions of anti-resorptive medications[118]. These results align with data from Sweden demonstrating an increased risk of fragility fractures in people with RA compared with the general population during the 1990s and 2000s, despite the expansion of pharmacological treatments for RA[119]. Overall, although the incidence of osteoporosis is declining, fracture rates have shown limited improvement in the RA population, suggesting that greater emphasis on fall-prevention strategies and patient counselling is warranted.

Pharmacological management

Despite advances in DMARD therapy, glucocorticoid exposure remains common in RA and continues to contribute to osteoporosis risk. With the increasing availability of DMARDs, a decline in glucocorticoid use was anticipated. However, data from Minnesota indicate that a greater proportion of people with RA initiated glucocorticoid therapy within the first 6 months of RA diagnosis between 2009 and 2018 compared with between 1999 and 2008, with no corresponding change in rates of glucocorticoid discontinuation[120]. Given that both the ACR and EULAR recommend that glucocorticoids be used at the lowest effective dose for the shortest duration, these findings highlight an opportunity to prioritize earlier glucocorticoid tapering as remission or low disease activity becomes more achievable with contemporary DMARD strategies[121,122]. Effective pharmacological therapies for the prevention and treatment of osteopenia and osteoporosis include calcium and vitamin D supplementation, as well as antiresorptive and anabolic osteoporosis therapies (such as bisphosphonates, denosumab and teriparatide)[123].

Preventive care

For osteoporosis risk assessment and to guide consideration of anti-osteoporotic therapy, the Fracture Risk Assessment Tool (FRAX) is recommended, because this tool is the only risk calculator that incorporates both a diagnosis of RA and glucocorticoid use[124]. Furthermore, the ACR has published guidelines on the prevention and treatment of glucocortoicoid-induced osteoporosis among individuals with rheumatic and non-rheumatic conditions[125]. These guidelines strongly recommend fracture-risk assessment using FRAX and evaluation of bone mineral density using dual-energy X-ray absorptiometry, including vertebral fracture assessment or spinal radiography, for people aged ≥40 years who are initiating or continuing glucocorticoid therapy at daily doses ≥2.5 mg for more than 3 months. For individuals aged <40 years, fracture-risk assessment can be performed using either dual-energy X-ray absorptiometry with vertebral fracture assessment or spinal radiography[125] (Table 1).

Conclusions

The increased burden of comorbidities in RA is well established. Encouragingly, advances in DMARD therapy and adoption of treat-to-target strategies have coincided with declining incidence of several non-severe extra-articular manifestations, CVD, CVA, dementia, overall malignancy, infection and osteoporosis. However, important gaps remain: ILD, anxiety and depression remain prevalent and require further investigation, because these comorbidities have not shown comparable improvements in epidemiological trends (Fig. 2).

Comorbidities in RA cannot be studied in isolation. Patterns of screening, prevention and management are influenced by evolving standards of care in the general population (Fig. 1). In parallel, treatments developed for metabolic diseases, such as type II diabetes mellitus (including metformin and glucagon-like peptide 1 receptor (GLP-1R) agonists), have garnered interest for their potential immunomodulatory effects in RA. However, current evidence remains largely observational[126,127], and rigorous randomized controlled trials are required to determine whether these agents meaningfully improve RA outcomes and to clarify their role within personalized treatment strategies for people with RA and coexisting metabolic disease. As new treatments for RA emerge, comparative effectiveness analyses will be essential to determine whether these therapies improve outcomes in this high-risk group, in whom comorbidity development is closely linked to chronic inflammation. Furthermore, structured care models — such

as early arthritis clinics and integration of dedicated comorbidity expertise — could support more comprehensive management of RA and its associated comorbidities[128].

Interpretation of the existing literature is limited by the predominance of cross-sectional and observational cohort studies. Although such designs are valuable for estimating prevalence, they do not permit causal inferences between RA and the incidence or risk of comorbidities, and residual confounding, including confounding by indication, remains a concern. To date, few randomized controlled trials have directly compared the effects of different classes of DMARDs on comorbidity outcomes. Furthermore, this Review could not address all RA-associated comorbidities, owing to a relative paucity of data on changing epidemiology trends for some conditions. Notable examples include periodontitis and adverse pregnancy outcomes, both of which have recognized associations with RA but remain under-studied in this context[129–131].

Ultimately, the treat-to-target approach to monitoring disease activity and modifying DMARD therapy to achieve remission or low disease activity should be central to RA care, because effective control of RA-related inflammation is imperative for reducing the risks of comorbidity[122]. DMARD selection should consider not only the disease characteristics, but also patient-specific comorbidities. Close collaboration between rheumatologists and primary care providers is necessary to improving outcomes in RA. Given the long-term consequences of systemic inflammation and the potential complications associated with DMARD therapy, further studies are needed to inform evidence-based cancer screening recommendations and to refine risk calculators for ILD and CVD in RA.

Published online: 29 May 2026

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Author contributions

C.S.C. and R.T.B. wrote the article. All authors researched data for the article, contributed substantially to discussion of the content, and reviewed and/or edited the manuscript before submission.

Competing interests

B.R.E. received research support from, and served as a consultant for, Boehringer-Ingelheim, and has consulted for Artive Biotherapeutics. The remaining authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Rheumatology* thanks Merete Hetland, Helga Lechner-Radner, Jianguang Ji and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Review criteria A literature search was conducted for original articles published between 2015 and 2025, focusing on meta-analyses, randomized controlled trials and cohort studies. Searches were performed using the terms "comorbidities" and "rheumatoid arthritis". Only full-text articles published in English were included. Reference lists of relevant articles were also screened to identify additional studies. Databases searched included EBM Reviews (Cochrane Central Register of Controlled Trials, Embase and Ovid MEDLINE (including Epub Ahead of Print and In-Process records). Searches covered publications from 2015 to 2025 and were last updated between April and May 2025.

nature reviews rheumatology

https://doi.org/10.1038/s41584-026-01381-7

Perspective

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Treat-to-target in Behçet syndrome

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Abstract

Behçet syndrome is a complex systemic immune-mediated form of vasculitis characterized by diverse clinical manifestations and a variable disease course. The treat-to-target (T2T) concept has emerged as a pivotal approach in managing various systemic autoimmune rheumatic diseases; however, its application in Behçet syndrome requires further work. Despite the limited literature on this subject, advancements from clinical trials have underscored the necessity for a T2T approach in Behçet syndrome. This article proposes an evidence-based perspective on the T2T strategy in Behçet syndrome, featuring a multidisciplinary and comprehensive collaboration of international experts, including rheumatologists, immunologists, ophthalmologists, gastroenterologists and neurologists. By adopting an organ-based approach to tackling crucial challenges, we aim to define treatment goals for organ involvement, discuss outcome measures that can be used as targets and definitions of remission and relapse, and also propose monitoring strategies (including treatment targets). The goal of this Perspective is to pave the way for future research and clinical practice, enhance the management of this complex condition and ultimately improve patient outcomes.

Sections

Introduction

Treat-to-target strategy for Behçet syndrome

Treat-to-target for mucocutaneous involvement

Treat-to-target for musculoskeletal involvement

Treat-to-target for ocular involvement

Treat-to-target for neuro-Behçet syndrome

Treat-to-target for vascular involvement

Treat-to-target for gastrointestinal involvement

Research agenda and future perspectives

Conclusions

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Introduction

Behçet syndrome is a rare, chronic, systemic form of vasculitis, which is also known as Adamantiades–Behçet disease or the Silk Road disease, owing to its peculiar geographical distribution[1–3]. The manifestations of Behçet syndrome can range from mild to life threatening, and are sustained by a complex and still largely unexplained pathogenesis, with features of autoinflammation and autoimmunity[4–12].

Disease onset peaks in the third decade of life, but it can manifest at any age, including childhood. Oral and genital ulcers are the most common sign and usually the earliest, and, together with eye lesions, represent the characteristic manifestations of the disease. However, the clinical spectrum is heterogeneous, and can include cutaneous, musculoskeletal, vascular, neurological and gastrointestinal involvement[4,13].

The disease has a variable, fluctuating and unpredictable course. Although mucosal manifestations usually present as non-serious relapsing–remitting phases, they can negatively impact health-related quality of life (HRQoL) and an increase in their frequency can lead to major organ involvement[14]. Ocular, neurological and vascular manifestations represent the major causes of disability and mortality in Behçet syndrome. Also, exposure to medications with potential severe adverse effects (such as high-dose glucocorticoids and immunosuppressants), increases the burden of morbidity, further reducing HRQoL[4].

Thus far, no validated laboratory, imaging or histological features unequivocally guide the diagnosis of Behçet syndrome, which relies on clinical assessment of signs and symptoms[15]. Moreover, the heterogeneity of the disease has hampered the development of a unique, valid and standardized method for scoring disease activity and defining standardized therapeutic targets (such as low disease activity (LDA) or remission)[16]. In this context, the application of a treat-to-target (T2T) strategy, an approach that is increasingly used in managing other systemic immune-mediated rheumatic diseases, is still far from routine clinical practice in Behçet syndrome.

T2T is a strategy in which clinical management decisions are directed to reach and maintain a pre-defined and sequentially measured target, typically through regular visits and sequential treatment adjustment. T2T is based on four key steps: defining the target; treating with the goal of achieving this target; testing regularly whether the target is achieved and if not, adjusting treatment[17,18]. Among immune-mediated rheumatic conditions, the T2T approach was first applied to rheumatoid arthritis (RA) over a decade ago[19,20] and evidence indicates that this approach is cost effective and can result in substantially better clinical and functional outcomes than usual care[21–26].

Over the past 10 years, the T2T approach has also been recommended for systemic lupus erythematosus (SLE)[27–29]. Notably, the application of T2T to a complex condition such as SLE is challenged by the absence of a unique disease activity marker, no clear definition of remission or LDA, the decision to take a general or single-organ approach to treatment, the complications of frequent disease monitoring and the need to optimize adherence to therapy[30–32].

Considering these experiences in RA and SLE, one could easily understand the challenges of defining and implementing T2T strategies in Behçet syndrome. Despite the limited literature on this subject, insights from clinical trials have underscored the necessity for a T2T approach in Behçet syndrome[33,34]. This article provides a perspective on the T2T strategy for Behçet syndrome, aiming to enhance the management of this complex condition in routine clinical practice and ultimately improve patient outcomes.

Treat-to-target strategy for Behçet syndrome

The management goals for Behçet syndrome are to obtain sustained drug-free remission without relapse and the prevention of damage to preserve function and HRQoL[35,36]. When working towards developing a T2T strategy, the first step is determining the targets that, when attained, best predict long-term success.

In the absence of validated definitions, prolonged remission in Behçet syndrome should be considered as sustained absence of disease activity over time. However, an evidence-based and standard definition of the required duration is not available and might need to be individualized according to risk factors for relapse such as the type of organ involvement, age, biological sex and disease duration. The advice in current guidelines is to continue immunosuppressive drugs for at least 5 years for manifestations such as vascular or nervous system involvement[36], but this indication should not be considered an evidence-based definition for the duration of sustained remission.

Similarly, relapse should be interpreted in an organ-specific manner and defined as recurrence of disease activity after remission. Disease activity can be difficult to differentiate from damage in Behçet syndrome and needs to be supported by objective findings. Clinical findings might be sufficient for mucocutaneous or musculoskeletal manifestations, whereas laboratory and/or imaging modalities might be required to confirm disease activity for organ manifestations[34,36].

Developing a T2T strategy for Behçet syndrome is more challenging than for some other immune-mediated rheumatic diseases owing to the heterogeneous organ involvement, variability in disease course and differences in organ manifestations in terms of frequency of relapses, treatment targets and tools for and frequency of monitoring[34–36] (Table 1). In other rheumatic diseases, composite measures for assessing disease activity are used to define treatment targets (such as Disease Activity Score-28 (DAS-28) in RA)[17,37]; however, tools that assess overall disease activity might be less suitable for Behçet syndrome owing to marked differences across organ domains. Currently available measures such as the Behçet's Disease Current Activity Form[38], lack weighting across organ manifestations, resulting, for example, in the same score in a patient with a single oral ulcer and a patient with a fatal pulmonary artery aneurysm. Although one could argue that complete remission with a score of '0' should be the target, the risks of escalating treatment to eliminate all mucocutaneous manifestations might outweigh the benefits, as a few occasional lesions are often acceptable to the patient and carry no long-term implications[39–41]. Thus, it is crucial to define clear organ-specific targets for Behçet syndrome that can predict long-term outcomes and can be assessed reliably and feasibly in terms of time and cost. We propose possible definitions of treatment targets for the involvement of different organ systems in Table 2. The involvement of different organ systems can require laboratory or imaging modalities to detect subclinical disease activity that can predict organ flares or long-term damage. Different monitoring approaches should be used for each organ system (Fig. 1). Importantly, evidence is needed to support the association between reaching treatment targets (such as obtaining remission or LDA) and the long-term goal of preventing damage and preserving HRQoL.

Treat-to-target for mucocutaneous involvement

Mucocutaneous lesions are the cardinal manifestations of Behçet syndrome. Oral ulcers are present in 92–100% of patients and usually precede other manifestations[39,40]. They are recurrent, can be painless or painful and heal without scarring. Genital ulcers are present in 55–95% of patients, are deeper and usually painful and can leave scars[40–42].

Table 1 | Proposed definitions of remission, disease activity, relapse and damage

Organ involvement	Disease activity	Remission	Sustained remission	LDA	Damage	Relapse
Mucocutaneous	Number of oral and genital ulcers and skin lesions; no validated score or defined time frame	Absence of active oral and genital ulcers or skin lesions; no defined time frame for assessment	Prolonged (no defined time frame) absence of active oral and genital ulcers or skin lesions	No consensus definition	Scars	Recurrence or new oral and genital ulcers or skin lesions following a period of remission
Musculoskeletal	Tender and swollen joint count (assessing all joints); no validated score or defined time frame	No tender and swollen joints	Prolonged (no defined time frame) absence of tender or swollen joints	No consensus definition	Destructive arthritis or functional impairment owing to recurrent or chronic synovitis	Recurrence of tender or swollen joints
Ocular	Presence of ocular inflammatory markers on biomicroscopy and fundus examination, capillary leakage on fluorescein angiography or macular oedema on OCT; no consensus on BOS24	Absence of inflammatory activity on biomicroscopy and fundus examination, dry fluorescein angiography and no macular oedema on OCT	Prolonged (no defined time frame) absence of inflammatory activity on biomicroscopy and fundus examination, dry fluorescein angiography and OCT	No consensus definition	Visual acuity loss, visual field defect, macular or optic nerve structural damage or irreversible retinal ischaemia	Recurrence of or increase in ocular inflammation or inflammatory markers
Nervous system	No validated measure and no validated definition of neuro-Behçet syndrome attack	No new neuro-Behçet syndrome clinical attacks or enhancing MRI lesions	Prolonged (no defined time frame) absence of neuro-Behçet syndrome clinical attacks or enhancing MRI lesions	Stable neurological function;no clear definition of function	Permanent neurological deficit, disability progression or residual MRI abnormalities reflecting irreversible CNS injury	New clinical attack or new or enhancing MRI lesions
Vascular (venous)	Presence of venous thrombosis at vascular imaging (Doppler ultrasonography or CT scan)	Venous recanalization	Prolonged (no defined time frame) absence of venous thrombosis	No progression of thrombosis and stabilization of venous flow abnormalities	Post-thrombotic syndrome	New or worsening venous thrombosis at vascular imaging (Doppler ultrasonography)
Vascular (arterial)	Presence of arterial lesions at vascular imaging (Doppler ultrasonography, PET or CT scan)	Disappearance of aneurysm or a reduction in size	Prolonged (no defined time frame) absence of arterial lesions	Stabilization (no progression) of arterial aneurysms or stenotic lesions	Irreversible vascular damage including aneurysm rupture, arterial occlusion with organ ischaemia or chronic vascular remodelling	New or worsening arterial lesion at vascular imaging
Gastrointestinal	Clinical activity (frequency, consistency and pain), stool calprotectin levels and endoscopic activity	Daily (≤3) normal stool consistency without bleeding or pain and mucosal healing at endoscopic assessment	Prolonged (no defined time frame) absence of lesions at endoscopic assessment	Recurrence of clinical symptoms or reappearance or worsening of ulcers on endoscopy	Fibrosis, strictures or postsurgical complications related to deep ulceration or perforation	New or worsening lesion at endoscopy and/or gastrointestinal clinical manifestations and/or increased levels of calprotectin

Timeframes for sustained (prolonged) remission are organ-specific. Shorter durations (such as 6–12 months) might be acceptable for mucocutaneous or musculoskeletal disease, whereas longer periods (up to 5 years) are generally required for major organ involvement before considering treatment de-escalation. BOS24, Behçet's Disease Ocular Attack Score 24; CNS, central nervous system; LDA, low disease activity; OCT, optical coherence tomography.

Other cutaneous lesions include erythema nodosum, papulopustular lesions, pseudofolliculitis and vasculitic lesions[39,40].

Clinical considerations

Mucocutaneous involvement usually occurs early in the disease course and substantially affects the HRQoL of people living with Behçet syndrome. The disease is typically chronic, characterized by cycles of exacerbation and remission[39,40]. Mucocutaneous manifestations are not life-threatening; however, they substantially decrease HRQoL owing to persistent pain, potential scarring, psychological and social distress and cosmetic appearance[39,43,44].

Measurement of disease activity for mucocutaneous involvement in Behçet syndrome is difficult. Although some tools have been proposed[45–48], they are not widely used in everyday clinical practice.

Table 2 | Proposed definitions of treatment targets

Organ involvement	Ideal target	Acceptable target
Mucocutaneous	Complete absence of active lesion	Reduction in number or frequency of lesions
Musculoskeletal	No tender or swollen joints, no inflammatory markers and no activity on ultrasonography	No tender or swollen joints
Ocular	No inflammation on biomicroscopy and fundoscopy, dry fluorescein angiography and no macular oedema on OCT	Absence of active retinal or optic disc inflammation
Neurological	Normal cognitive or physical function and disappearance of MRI lesions	Stable neurological function and no worsening of MRI lesions
Vascular (arterial)	Disappearance or reduced size of pulmonary aneurysm	Stable size and no rupture
Vascular (venous)	Recanalization	No progression
Gastrointestinal	Endoscopic remission	Clinical improvement and reduced calprotectin

Timeframes for sustained remission are organ-specific. OCT, optical coherence tomography.

In most studies, activity is assessed by the presence and the number of mucosal ulcers and skin lesions; severity, pain, frequency and healing time are also considered[49]. Remission of mucocutaneous involvement in Behçet syndrome is defined by the complete absence of active lesions. Although consensus has not yet been achieved, a relapse can be defined as the recurrence or new emergence of disease manifestations following a period of remission. Relapses can vary in severity, and not all require escalation to systemic therapy.

In patients with mucocutaneous involvement, clinical examinations, patient-reported symptoms and dermatological assessments at regular intervals for refractory or severe disease (for example, every 6 months or earlier during symptomatic periods) are essential. We advise that documentation of lesions (such as by taking photographs) can also be useful in monitoring disease course, identifying subtle changes and facilitating communication with health care providers.

Treatment

Colchicine is the standard initial treatment for mucocutaneous manifestations. Azathioprine is also a therapeutic option, but for people with severe and/or refractory disease, TNF inhibitors can be considered[35,36]; the evidence base is strongest for infliximab, etanercept and adalimumab[50–52]. However, these data are mainly derived from observational studies rather than from randomized trials[52,53]. A PDE-4 inhibitor (apremilast) was approved for oral ulcers in Behçet syndrome, after a 12-week randomized, placebo-controlled phase III trial (RELIEF) involving 207 adults showed a reduction in oral ulcers (area under the curve 129.5 versus 222.1, for apremilast and placebo, respectively; $P < 0.001$) and improved pain and HRQoL scores[54]. Favourable results were maintained up to week 64 (ref. 55). Real-world studies also report improvement in oral and genital ulcers, with similar response rates between apremilast and TNF inhibitors[56,57]. Moreover, in two prospective non-comparative, non-randomized observational studies of patients treated with the IL12–IL-23 inhibitor (ustekinumab), improvements in the number of mucocutaneous manifestations, oral-ulcer pain and glucocorticoid sparing were reported[58,59]. Some evidence from small studies suggests that IL-17 inhibition (secukinumab) might be effective for refractory mucocutaneous involvement[60,61]. However, more studies that include people with bowel involvement are needed as inhibition of IL-17 might lead to adverse effects.

Treatment intensification is guided by persistent active lesions despite ongoing therapy. Conversely, dosage reduction or treatment discontinuation can be considered when prolonged remission (generally >6–12 months) is achieved, albeit cautiously owing to relapse risks. Evidence suggests that cautious withdrawal of TNF inhibitors can lead to prolonged remission in a subset of patients, but relapse rates necessitate vigilant monitoring and readiness for prompt reintroduction of therapy upon relapse[62].

Overall, these factors combined indicate that a T2T approach could lead to stable control of mucocutaneous involvement in Behçet syndrome, but the implementation of this approach first requires consensus definitions on treatment goals and on the timing of their assessment.

Treat-to-target for musculoskeletal involvement

Musculoskeletal manifestations are present in 40–70% of patients and can precede, coincide with or follow other manifestations[4,44]. Arthritis in this context is typically non-erosive and non-deforming, typically presenting as monoarthritic or asymmetric oligoarthritis, commonly involving the knees, ankles, wrists and elbows[63].

Clinical considerations

Arthritis episodes are usually transient, lasting days to weeks, with prognosis being generally favourable, characterized by intermittent flares and prolonged remission periods. Symptoms (such as chronic joint pain) can affect mobility, daily functioning and HRQoL, but they rarely cause permanent joint damage and permanent deformities are uncommon[49,63–65]. Measurement of musculoskeletal disease activity involves assessing joint pain and swelling. Currently, no validated tool exists to measure disease activity, but the classic tender and swollen joint counts used in RA and psoriatic arthritis have been successfully used in trials of Behçet syndrome[66]. Given that lower-extremity joints are predominantly affected in Behçet syndrome, assessment of all joints rather than only the 28 joints measured for the DAS-28 score is encouraged. In this setting, remission can be defined as the absence of tender and swollen joints. We propose that relapse can be defined as recurrence of arthritis after a period of remission, particularly when associated with objective joint swelling.

In patients with musculoskeletal involvement, clinical evaluation, including joint examination and patient-reported symptoms of pain and functional capacity (for example, every 3–6 months) is advised. Imaging modalities such as ultrasonography or MRI can be used in certain instances, especially when more objective evidence of joint involvement and/or exclusion of other pathologies is needed[64,65].

Treatment

Colchicine is also the standard initial treatment for musculoskeletal involvement and azathioprine is a therapeutic alternative. For arthritis, NSAIDs or glucocorticoids can also be used[35,36]. For people with severe or refractory disease, TNF inhibitors can be effective for musculoskeletal manifestations[35,36] (similar to mucocutaneous manifestations, the most evidence available is for infliximab, etanercept and adalimumab[50–52]). Some evidence also indicates that blocking IL-17, IL-12–IL-23 or PDE-4 might improve arthritic involvement[60,61,66,67]. Treatment

intensification is guided by persistent joint symptoms despite ongoing therapy. Dosage reduction or treatment discontinuation can be considered cautiously (owing to relapse risk) when sustained remission (>6–12 months) is achieved.

In this context, a T2T approach might improve therapeutic and clinical outcomes in patients with musculoskeletal involvement, pending the development of a validated tool to measure disease activity, and consensus definitions of modalities and optimal timing for disease monitoring.

Treat-to-target for ocular involvement

Ocular involvement can present in numerous ways; however, uveitis and neuro-ophthalmological conditions are among the most clinically important presentations[68–70]. Uveitis occurs in 35–60% of people with Behçet syndrome and can be the first manifestation in around 20%[71–73].

Clinical considerations

Panuveitis is the most frequent presentation, typically accompanied by non-granulomatous anterior inflammation, vitritis, papillitis, retinal necrosis, vasculitis and vascular occlusions. Isolated anterior uveitis with hypopyon is rare. Macular oedema, epiretinal membrane, macular hole, retinal ischaemia and cataract are possible complications. The disease is usually bilateral at onset or can become bilateral within the first 2 years and can be associated with blindness or visual impairment in approximately 15% of patients, although this rate has decreased over the past 20 years owing to earlier diagnosis and therapeutic progress, especially the use of biologic agents[74–76]. The disease often affects young and active patients and must be treated for many years to avoid relapses and permanent visual loss. Compared with other types of uveitis, retinal necrosis that involves the macula can be unpredictable, inducing permanent visual loss, despite aggressive therapy[77].

Ocular disease activity is assessed by measuring inflammatory markers, which can be easily detected and quantified using slit-lamp biomicroscopy, fundus examination and multimodal imaging[78]. The level of anterior chamber flare and vitreous haze are the easiest biomarkers to evaluate. Wide-field fundus photography, fundus fluorescein angiography (fern-like pattern) and optical coherence tomography (OCT) are of utmost importance for posterior segment evaluation[78,79]. All inflammatory markers must be resolved to achieve remission. Remission is assessed based on biomicroscopy findings in the anterior chamber and vitreous, and, according to the authors, can be defined as no active lesions on fundus examination and dry fluorescein angiography, and no macular oedema on OCT. Laser flare photometry can be used to evaluate the level of anterior chamber flare correlating with posterior segment activity[80]. A proposed definition of relapse is the recurrence of ocular inflammatory activity after remission, as documented clinically and/or by multimodal imaging, including new inflammatory lesions on fundus examination, angiographic leakage on fluorescein angiography or macular oedema on OCT.

Clinical tools and multimodal imaging are used for disease monitoring. OCT with angiography is a promising non-invasive tool, but it cannot replace fluorescein angiography[81]. The timing of ocular monitoring remains variable depending on the severity of ocular involvement and complications. Ocular disease should be monitored monthly prior to achieving remission. Patients must be informed of the main clinical symptoms that might suggest a relapse. In patients who have achieved remission, the same tools are used for monitoring, with a progressively lower frequency (quarterly and then half-yearly)[81]. Invasive procedures such as fluorescein angiography can be proposed once or twice a year, depending on the clinical patterns. OCT and visual-field evaluation are important for detecting macular, optic nerve or central nervous system (CNS) complications. Scores such as the Behçet's Disease Ocular Attack Score 24 (BOS24) can predict ocular changes[82,83], but must be completed with fluorescein angiography, even after achieving remission.

Treatment

Management of ocular disease requires close collaboration between ophthalmologists, rheumatologists and internists[36,84]. Isolated anterior uveitis can be treated with topical or periocular glucocorticoids; however, in young men with early disease onset, the risk of posterior involvement justifies the use of systemic immunosuppressants[36,84]. In all other types of Behçet uveitis, conventional immunosuppressants

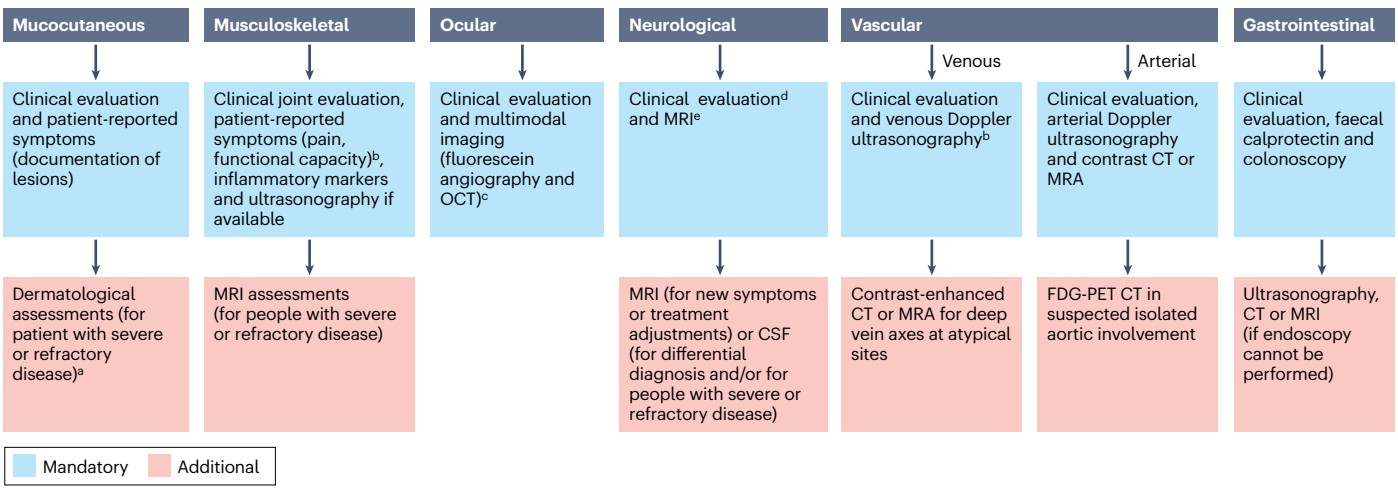

Fig. 1 | Proposed mandatory and additional disease assessments. An overview of the clinical and diagnostic assessments that should be considered for all patients with Behçet syndrome who have organ system involvement (defined as 'mandatory' assessments) and additional assessment for certain patients (for example, patients with more severe or refractory manifestations). The proposed timing for the different assessments is also noted. FDG-PET-CT, fluorodeoxyglucose-PET-CT; MRA, magnetic resonance angiography; OCT, optical coherence tomography.

and biologic agents such as monoclonal anti-TNF antibodies (particularly infliximab) or IFNα are mandatory[36,85–89]. Glucocorticoids (either systemic or intravitreal) are used only in combination with immunosuppressants, and never alone; in particular, intravitreal glucocorticoids can be used for unilateral relapses in addition to systemic therapy[36]. In a Chinese randomized controlled trial (RCT), adalimumab plus glucocorticoids was superior to cyclosporin plus glucocorticoids for uveitis relapse rate in patients naive to anti-TNF treatment[90]. For people with immediate visual threat, high-dose glucocorticoids or infliximab are recommended[36]. The use of azathioprine or cyclosporin A together with biologic drugs can provide additional benefits over biologic drug monotherapy, although no RCTs have evaluated this aspect and observational studies report conflicting results[91,92]. Local vascular endothelial growth factor inhibitors can be used for patients with neovascular complications associated with diffuse retinal ischaemia[93]. Rarely, laser photocoagulation of the retina might be required. Vitrectomy (that is, the surgical removal of the vitreous humour from the eye cavity) can be used for chronic intravitreal haemorrhages, surgical macular or retinal complications[93]. At least 2 years of sustained remission without relapse is generally required before considering treatment tapering, although longer periods can be preferable for patients with severe posterior segment involvement[94].

In this context, the routine implementation of a T2T approach has the potential to improve long-term visual outcomes of ocular Behçet syndrome.

Treat-to-target for neuro-Behçet syndrome

Neuro-Behçet syndrome is one of the most severe manifestations of Behçet syndrome. Parenchymal disease (which typically affects the mesodiencephalic junction, pons and medulla) is the predominant form. Cerebral venous sinus thrombosis is the second most common manifestation.

Clinical considerations

CNS involvement is the primary determinant of long-term disability in neuro-Behçet syndrome[95]. Patients presenting with motor-predominant symptoms are at the highest risk of permanent neurological sequelae, underscoring the crucial need for early and effective suppression of CNS inflammation[96]. Cerebral venous sinus thrombosis generally carries a favourable prognosis when recognized and treated promptly[96]. A major challenge in the management of neuro-Behçet syndrome is the absence of validated, disease-specific outcome measures and attack definitions. Existing criteria have been largely adapted from multiple sclerosis; however, fundamental differences between the two diseases limit their applicability[97]. Neuro-Behçet syndrome attacks are often more severe and disabling, subclinical activity at MRI is rare and disease activity is almost always clinically overt[96]. Moreover, standardized definitions for attacks, pseudo-attacks and pseudo-progression are lacking[98]. This gap complicates treatment decisions and outcome assessment, contributing to the risks of both overtreatment and undertreatment.

In autoimmune neurology, the concept of no evidence of disease activity (NEDA) has revolutionized the care of multiple sclerosis, by emphasizing remission defined as the absence of relapses, MRI activity and disability progression[99]. In practical terms, we propose that remission can be considered as sustained clinical stability without new neurological attacks, no new or enhancing MRI lesions and no progression of neurological disability.

Consultation with an experienced neurologist is helpful, as progression — although uncommon — can occur and is often related to accumulated damage, aging or comorbidities rather than active disease[95,96]. Although the concept is not formally applied to neuro-Behçet syndrome, disease progression in some instances can resemble pseudo-progression described in other autoimmune disorders.

Until validated attack definitions, disease-specific outcome measures and objective biomarkers become available for neuro-Behçet syndrome, a tailored, NEDA-inspired approach, centred on clinical stability, selective imaging and long-term biologic drug therapy, offers a pragmatic and evidence-based framework for optimizing care. We propose that the optimal treatment targets in neuro-Behçet syndrome are the sustained absence of new clinical attacks, no new or enhancing MRI lesions and stable neurological function over time.

Our proposed definition of relapse is a new clinically meaningful neurological event attributable to active disease, which is usually accompanied by new or enhancing MRI abnormalities. However, isolated residual MRI changes in patients who are clinically stable should be interpreted with caution.

Unlike multiple sclerosis, in which silent MRI lesions often guide therapeutic adjustments, such findings are rarely observed in neuro-Behçet syndrome; thus, clinical evaluation remains the cornerstone of disease monitoring[100]. During active disease, follow-up should be performed frequently (such as every 1–2 months) with particular attention to motor, brainstem and cognitive function. In parenchymal neuro-Behçet syndrome, the authors suggest that an MRI performed 4–6 weeks after treatment initiation can confirm the radiological efficacy of treatment (such as high-dose intravenous glucocorticoids). The resolution of the lesion(s) and contrast enhancement can assist both in assessing the response to treatment and in differentiating neuro-Behçet syndrome from other conditions, such as CNS tuberculosis, particularly in patients receiving infliximab[101]. Beyond monitoring treatment response, imaging should be reserved for new clinical events or deterioration. Once remission is achieved, clinical evaluations are generally sufficient every 6 months, with MRI undertaken only if new symptoms develop or treatment adjustments are contemplated. Biomarkers such as neurofilament light chain and glial fibrillary acidic protein might, in the future, provide objective measures of disease activity and support T2T strategies, although validation in neuro-Behçet syndrome is still ongoing[102].

Treatment

The primary aim of treatment in neuro-Behçet syndrome is rapid control of CNS inflammation and sustained prevention of relapses. TNF inhibitors, particularly infliximab and adalimumab, have emerged as the cornerstone of maintenance therapy[36]. Conventional immunosuppressants such as azathioprine, methotrexate and cyclophosphamide were historically used, but are now considered secondary options. Although no robust evidence is available, the concomitant use of azathioprine and TNF inhibitors can provide additional benefits over biologic drugs alone, particularly by reducing immunogenicity and maintaining treatment in the event of delays in biologic drug supply[36]. However, immunogenicity in Behçet syndrome seems to be less common than in other diseases such as RA[103]. Treatment with TNF inhibitors is generally well tolerated, but requires pre-treatment screening, particularly for latent tuberculosis, and careful long-term monitoring[104].

Treatment escalation should be considered only when true disease activity or progression is confirmed. Careful clinical judgment is required to distinguish genuine inflammatory activity from transient symptom fluctuations or unrelated comorbidities. Dose optimization

can be considered before switching to an alternative biologic agent, but drug discontinuation is generally not advised, as relapses can occur even after prolonged stability leading to irreversible neurological damage[62].

In neuro-Behçet syndrome, treatment decisions should be primarily driven by clinical activity. Residual MRI abnormalities in the absence of clinical symptoms might reflect structural damage rather than ongoing inflammation. In the absence of robust evidence, a pragmatic approach is to maintain therapy for at least 5 years in patients with major organ involvement[35,36]. In those with sustained clinical remission and no evidence of active disease, we advise considering cautious tapering, preferably withdrawing conventional immunosuppressants before biologic agents. For patients receiving combination therapy, tapering of conventional immunosuppressive agents before biologic agents might be preferred.

Overall, treatment decisions and adjustments in neuro-Behçet syndrome should follow a T2T strategy, based on standardized disease activity monitoring.

Treat-to-target for vascular involvement

Behçet syndrome can involve both arterial and venous vessels of all sizes, which makes it unique among vasculitides. Vascular involvement occurs in up to 20–30% of patients and is a potentially severe complication of Behçet syndrome[105,106]. Venous involvement is more frequent than arterial in Behçet syndrome and is caused by inflammatory thrombosis rather than a hypercoagulable state.

In addition to vascular involvement, cardiac manifestations have been reported in 5–8% of patients[107,108]; however, evidence remains limited and largely derived from small series and observational cohorts. Given the paucity of robust data and the absence of validated outcome measures for cardiac disease, the present discussion of T2T strategies focuses on vascular involvement only.

Clinical considerations

Three-quarters of patients experience their first vascular event within 5 years of disease onset[105]. This involvement can develop before or simultaneously with mucocutaneous lesions in about one third of patients[105,106]. The disease course is relapsing, and relapses occur mainly at the primary site or at another vascular region, causing extensive involvement. Vascular phenotype frequently manifests with fever, high acute phase response and constitutional symptoms[105,106,108].

Deep vein thrombosis is the most common vascular manifestation, typically involving the lower extremities; superficial thrombophlebitis can also occur. Vena cava thrombosis and Budd–Chiari syndrome are associated with severe morbidity and mortality[109]. Arterial lesions are less common (3–5% of patients), but might be life threatening[105]. Pulmonary artery aneurysms are characteristic and highly specific to Behçet syndrome, exposing patients to a potential risk of haemoptysis and rupture[110]. Aneurysms can also affect the aorta and the femoral and iliac arteries. Arterial thrombosis and occlusion can cause ischaemia, infarction or limb claudication. Coronary-artery involvement is rare, but can cause myocardial infarction. The mortality rate of arterial manifestations can reach up to 26%; patients who develop arterial involvement have up to a 2.5-times higher risk of death than those without these manifestations[111].

Vascular-disease activity refers to the presence of signs and symptoms that indicate ongoing inflammation or thrombosis in blood vessels. Clinical symptoms such as fever, limb pain, swelling, ischaemic signs, haemoptysis (in pulmonary artery aneurysm), laboratory markers such as elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) often support clinical findings, but are not definitive alone. We propose defining active vascular disease as vascular imaging (Doppler ultrasonography, CT angiography or MR angiography) that shows new or worsening venous thrombosis, the development of new arterial aneurysms, new arterial thrombosis or stenosis.

We suggest that remission can be defined as the absence of clinical signs and symptoms attributable to Behçet syndrome, normalization of inflammatory markers, no new vascular lesions at imaging and no progression of existing lesions at imaging. Thus far, no consensus has been reached for what defines remission on vascular imaging. Ideally, remission on imaging could be defined as the disappearance or reduction in size of arterial aneurysms or recanalization of arterial and deep vein thrombosis. However, arterial aneurysms in some patients do not decrease in size, despite effective suppression of inflammatory activity. In one RCT, remission on imaging was defined as an absence of new lesions in previously unaffected vascular territories and the absence of progression of pre-existing vascular lesions detected on serial imaging studies (that is, vascular Doppler ultrasonography, CT angiography or MR angiography)[112]. Similarly, in a large cohort study of patients with vascular involvement remission was defined as 'lack of worsening of the primary vascular lesion and a new lesion at another vascular site on imaging'[113]. Thus, a patient whose vascular manifestations are stable on imaging can be in considered in remission if they have no clinical or laboratory findings suggesting active disease. Recanalization of thrombus can be even more challenging in Behçet syndrome, hence why using recanalization as a treatment target is still debated[105,108].

Vascular damage refers to the occurrence of post thrombotic syndrome, pulmonary hypertension or optic atrophy as a consequence of cerebral hypertension[114]. We propose defining relapse as the recurrence of active vascular involvement after remission, supported by objective evidence such as new thrombosis, new aneurysm formation, progression of existing vascular lesions on imaging or recurrence of vascular symptoms attributable to active inflammation (such as pain, swelling or inflammatory signs along the affected vessel).

Venous Doppler ultrasonography is the most commonly used imaging tool for detecting venous involvement of lower extremities. Contrast-enhanced CT scan and MR angiography as non-invasive radiological methods are used alongside Doppler ultrasonography to analyse deep arterial and vein axes. Fluorodeoxyglucose (FDG)-PET-CT can also be an option for patients with Behçet syndrome and suspected isolated aortic involvement. Disease monitoring with clinical, laboratory and vascular imaging is mandatory (such as every 3–6 months initially, then vascular imaging performed annually). In life-threatening and severe situations closer monitoring is required.

Treatment

Glucocorticoids are the cornerstone of induction therapy. High-dose intravenous methylprednisolone pulses or oral prednisone (1 mg/kg per day) are used in acute severe vascular disease (such as pulmonary aneurysms and Budd–Chiari syndrome)[35,36].

TNF inhibitors, particularly infliximab, are the key maintenance therapy, as they can induce complete remission, reduce relapses and stabilize disease, especially in patients with severe disease[112]. Cyclophosphamide might be used as an alternative for severe vascular disease. Anticoagulation in venous thrombosis in Behçet syndrome is controversial as thrombosis occurs because of vasculitis. Most experts

recommend considering anticoagulation if thrombosis is extensive, life-threatening, persistent or relapsing, despite immunosuppression, provided that the risk of bleeding is low and coexistent pulmonary artery aneurysms have been ruled out[36].

Elective endovascular interventions or surgery should be performed in phases of stable remission. Arterial vessel dissection, life-threatening arterial aneurysms or critical vascular ischaemia requires urgent referral to an expert vascular team. All these procedures are usually performed after controlling inflammation with immunosuppressants[115,116].

Given the severity of vascular Behçet syndrome and the risk of severe relapse, we advise that treatment tapering should be approached with caution and generally considered only after prolonged remission, typically after at least 4–5 years in patients with major organ involvement, particularly for those with arterial disease or previous severe events[36]. Glucocorticoids can be tapered first, continuing DMARDs or biologic drugs for longer periods.

The complexity of vascular involvement in Behçet syndrome highlights the need to develop a set of treatment goals and monitoring approaches that can capture the different spectrums of arterial and venous events to effectively implement a T2T approach.

Treat-to-target for gastrointestinal involvement

The most common symptom in gastrointestinal Behçet syndrome is right lower quadrant abdominal pain, with less frequent occurrences of mild-to-moderate diarrhoea[117].

Clinical considerations

Gastrointestinal bleeding is rarely the initial sign of Behçet syndrome, but up to 30% of patients can develop complications such as overt bleeding or perforation, either before or after diagnosis of Behçet syndrome[117,118]. Characteristic ulcers are typically few in number (less than 5), deep (>1 cm), oval and located in the ileocaecal region[117,119]. The prevalence of gastrointestinal involvement in patients with Behçet syndrome varies by region, estimated as being 15–25% in Japan, 10–15% in Korea and the Middle East and ~1% in Turkey[120].

Diagnosis relies on typical or atypical ulcers and partial or complete fulfilment of Behçet syndrome criteria, categorized as definite, suspected or probable[118,121]. In established Behçet syndrome, ulcer complication potential (size, depth or volcano type) can outweigh atypical morphology[122]. Histological evidence of vasculitis is rare in punch biopsy-obtained mucosal samples, primarily owing to superficial sampling and the early disappearance of vasculitic features, which usually precedes the development of the clinically overt ulcers[117,118].

Gastrointestinal involvement in Behçet syndrome (similar to Crohn's disease) typically involves the ileocaecal region, but in Behçet syndrome large, deep volcano-type ulcers that are prone to bleeding or perforation occur in up to 30% of patients, whereas in Crohn's disease, linear and star-shaped ulcers are more typical[119,120]. Gastrointestinal tuberculosis can mimic both gastrointestinal manifestations in Behçet syndrome and Crohn's disease, especially in endemic areas (such as Turkey, Iran, the Middle East and East Asia)[120–122]. Granulomas in biopsies indicate gastrointestinal tuberculosis or, less frequently, Crohn's disease, but not gastrointestinal involvement in Behçet syndrome[123]. Ulcers in the oesophagus, stomach or duodenum should only be attributed to gastrointestinal involvement in Behçet syndrome after excluding other causes such as the use of NSAIDs, colchicine or infections, even if Behçet syndrome criteria are met[120,124]. Before attributing rare oesophageal or gastric lesions to Behçet syndrome, viral triggers (such as cytomegalovirus or herpes simplex virus) and drug-induced (for example, NSAIDs or colchicine) ulcers should be excluded[120,125].

Periodic fever with abdominal pain can suggest coincidence of familiar Mediterranean fever or haematological disorders such as trisomy 8 myelodysplastic syndrome, acute myeloid leukaemia or acute lymphoblastic leukaemia. Notably, up to 70% of these patients meet Behçet syndrome criteria, but respond only to haematological treatments[126]. Children with early, aggressive, treatment-resistant ulcers might have monogenic disorders such as HA20 or IL-10 or IL-10 receptor deficiency. These conditions can mimic incomplete gastrointestinal involvement in Behçet syndrome, even into adulthood[127,128].

Poor clinical outcomes are linked to high C-reactive protein, complications at onset or follow-up, younger age, male biological sex, glucocorticoid dependency and HLA-B51-positivity[118,122]. In addition, volcano-type ulcers carry a high risk of complications[118,122,123].

Right lower quadrant pain often remains the primary symptom. As gastrointestinal involvement in Behçet syndrome tends to involve fewer ulcers and is usually more localized than Crohn's disease, diarrhoea tends to be milder. Indices such as the Crohn's Disease Activity Index and Disease Activity Index for Intestinal Behçet's Disease are mainly research tools[129]. Clinically, remission is defined as ≤3 stools per day of normal consistency without bleeding or abdominal pain; however, as symptoms can underestimate ongoing intestinal inflammation, remission should ideally be supported by endoscopic healing, particularly in patients with large, deep volcano-type, high-risk ulcers[130].

We propose that relapse can be defined as the recurrence of gastrointestinal symptoms attributable to active disease, particularly when associated with endoscopic reappearance or worsening of ulcers, new gastrointestinal bleeding or worsening symptoms that require treatment escalation. Colonoscopy is preferred for disease monitoring unless obstruction is suspected; otherwise, cross-sectional imaging (ultrasonography, CT or MRI) is used. Endoscopic monitoring is essential until mucosal healing occurs, especially for high-risk ulcers. Disease flares should always prompt endoscopic reassessment. Stool calprotectin can help to monitor disease activity, especially when interpreted alongside prior colonoscopy findings, but it cannot replace endoscopic evaluation[131,132].

Treatment

Glucocorticoids relieve symptoms quickly, but flares are common during tapering[120,133]; anti-TNF agents should be started during tapering for high-risk disease. 5-aminosalicylic acid might work for mild disease or aphthous ulcers. Deep or volcano-type ulcers often require anti-TNF agents[134–136]. Azathioprine can be combined with anti-TNF agents to reduce antibody formation[36,137]. In patients who initially respond to anti-TNF agents but later experience a relapse of symptoms, an increased dose can be considered. For those who do not respond to anti-TNF agents, switching to JAK inhibitors is advised[138,139]. Thalidomide can be considered as a last resort and should be used with extreme caution; monitoring potential adverse effects is particularly important for patients of reproductive age[140].

In patients with refractory disease regimens used for inflammatory bowel disease can be considered as second- or third-line options for Behçet syndrome[36,117]. As spontaneous clinical remission and reactivation of gastrointestinal involvement can occur in Behçet syndrome, we advise that treatment de-escalation under endoscopic guidance can be attempted for patients with long-term clinical and endoscopic remission (≥2 years), especially for uncomplicated disease[36]. For those receiving combination treatment, the best approach would be to stop

treatments one at a time under endoscopic surveillance, leaving a 1-year interval between discontinuation of each drug.

Surgery is reserved for complications such as perforation, bleeding or obstruction. Partial resection might be necessary for localized disease. Reoperation rates are high (25% at 2 years and 50% at 5 years)[141]. We highlight that pathergy-like reactions at anastomosis sites raise the relapse risk; thus, continued or intensified medical therapy is often needed postoperatively. Temporary or permanent stoma might be required or mandatory for patients with severe complications, such as repeating perforations or severe bleeding.

The implementation of a T2T approach for gastrointestinal involvement in Behçet syndrome has the potential to improve long-term clinical outcomes, by targeting endoscopic remission from the beginning and reducing the burden of (re)operation and permanent complications.

Research agenda and future perspectives

Future research in Behçet syndrome should focus on a set of interconnected priorities that are essential for enabling a T2T strategy. A central unmet need is the development of validated and standardized definitions of remission, sustained remission, LDA, relapse and damage, across all disease domains (Table 1). Without such shared terminology, it remains difficult to establish consistent treatment targets or to compare outcomes across studies and clinical settings. Parallel to this effort, refined organ-specific measures of disease activity and remission, together with composite tools that capture the systemic nature of Behçet syndrome and incorporate patient-reported outcomes (including fatigue, psychological wellbeing, physical functioning and work ability), are required to ensure that clinically relevant changes can be reliably detected. Concomitantly, the management of comorbidities that can influence the long-term, positive outcomes also need to be ensured.

As disease monitoring represents a cornerstone of any T2T approach, research should clarify the optimal timing and frequency of assessments for each phenotype, and the relative value of clinical examination, laboratory markers and imaging modalities in predicting relapses and long-term damage. The heterogeneity across organ domains underscores the need for longitudinal studies that can determine which tools are most responsive and feasible in routine practice, and how monitoring schedules can be adapted once remission is achieved (Table 2, Fig. 1).

Advances in biomarkers and digital health technologies offer promising avenues to support early detection of disease activity and individualized treatment adjustments. Objective serum, cerebrospinal fluid and imaging biomarkers, together with emerging molecular and microbiome signatures, warrant systematic evaluation, as do digital tools that enable real-time symptom tracking, medication adherence monitoring and remote assessment of patient-reported outcomes. These tools might assist in risk stratification, which is needed to determine those patients who need to be treated more aggressively upon diagnosis. Multinational randomized trials and pragmatic prospective cohorts with broader geographic representation will be essential to ensure that proposed treatment targets are feasible, safe, cost-effective and acceptable across diverse populations and health care systems.

The marked clinical heterogeneity of Behçet syndrome poses intrinsic challenges to trial design. The frequency of organ involvement varies across geographic regions, with ocular disease being among the most common manifestations globally, gastrointestinal involvement showing regional variability and neurological involvement remaining relatively rare[1,2,4]. These differences, together with the overall rarity of the disease, limit the feasibility of adequately powered, organ-specific trials outside high-prevalence regions or highly specialized referral centres. Although the majority of RCTs and cohort studies of treatments published thus far have focused on specific organ manifestations, robust data supporting organ-targeted treatment strategies remain scarce for rare manifestations such as gastrointestinal and nervous system involvement. Treatment decisions are mainly based on open label, uncontrolled studies for these manifestations. Robust comparative evidence is needed to define optimal therapeutic strategies within a T2T framework. A key priority is to determine whether an upfront intensive strategy using anti-TNF agents, or a step-up approach, starting with conventional therapies and escalating only for those with refractory disease, leads to improved treatment outcomes and sustained long-term benefit across specific organ phenotypes. Also, the usefulness of combination therapies versus monotherapy should be determined for both remission induction and maintenance, together with safe approaches to dose reduction or discontinuation in patients with stable remission. The individual preferences of the patient should be considered, and an efficient use of resources and treatment modalities should be ensured. Addressing disparities between countries in terms of health care systems and reimbursement policies, as well as individual prognostic factors such as biological sex, age and disease duration, are also within the scope of a T2T strategy.

Together, these research directions form the foundation for implementing an effective and widely applicable T2T strategy in Behçet syndrome, the ultimate goal being to reduce irreversible organ damage and improve long-term outcomes.

Conclusions

A T2T approach is necessary to optimize the management of Behçet syndrome, ensuring an efficient use of novel therapeutic options and improving clinical and patient-reported outcomes. Future multidisciplinary and multinational efforts that include patient research partners are required to develop validated composite outcome measures, establish consensus definitions of treatment targets and identify biomarkers and digital health tools for disease monitoring. Also, high-quality evidence from RCTs comparing T2T strategies with routine care in terms of efficacy, cost and feasibility, and pragmatic real-world studies are necessary to facilitate the future inclusion of a T2T approach in guidelines and its adoption in clinical practice.

Published online: 21 May 2026

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Acknowledgements
Part of the discussion that prompted this Perspective article arose during the 4th International Society for Behçet's Disease (ISBD) webinar on 'Treat to target in Behçet's syndrome' chaired by G.H. and P.P.S. (30 January 2025). This Perspective was developed within the ISBD Study Group on Epidemiology.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
B.B. has received consulting fees from AbbVie, Alimera, Horus Pharma, Novartis and Roche. G.B. has received research grants, speaker fees and/or consulting fees from MSD, AstraZeneca, GSK, AbbVie, Lilly, Boehringer, Ostuka and UCB. G.E. has received research grants, speaker fees and consulting fees from GSK, AstraZeneca, SOBI and Novartis. G.H. has received research grants, speaker fees and consulting fees from AbbVie, Amgen, Johnson & Johnson, MSD, Novartis, Soligenix and UCB Pharma. P.P.S. has received research grants, speaker fees and consulting fees from AbbVie, Amgen, Boehringer, Eli-Lilly, Elpen, Genesis, GSK, Johnson & Johnson, MSD, Novartis, Pfizer and UCB Pharma. All other authors declare no competing interests.

Additional information
Peer review information *Nature Reviews Rheumatology* thanks Vanesa Calvo-Río, Jian-Long Guan and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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